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Journal of The Chemical Society

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Mortimer, C. T. See Cass, R. C., 1406
Muray, J. See Dickinson, F., 1441
Nicholls, D. See Fowles, G. W. A., 1687
Nunn, E. K. See Friend, J. A., 1567
Ogilvie, G. S. See Fischer, A., 1426
Onyszchuk, M. See Ebsworth, E. A. V., 1453
Osborne, G. O. See Baddiley, J., 1651
Ottewill, R. H. See Few, A. V., 1712
Packer, J. See Fischer, A., 1426
Packer, J. E. See Fischer, A., 1426
Pai, B. R. See Govindachari, T. R., 1715
Parken, E. R. See Hunter, R. F., 1561
Parkins, G. M. See Le Fèvre, C. G., 1468
Parreira, H. C. See Few, A. V., 1712
Pearce, M. L. See Griffiths, V. S., 1557
Percival, E. See Gardiner, J. G., 1414
Petrow, V., Stephenson, O., Thomas, A. J., and Wild, A. M., 1508
Petrow, V. See also Kirk, D. N., 1334
Phillipps, G. H. See Evans, R. M., 1529
Pinchas, S. See Halmann, M., 1703
Potter, M. D. See Austin, W. C., 1489
Quartey, J. A. K., 1710
Rao, B. P. See Le Fèvre, R. J. W., 1465
Rivlin, V. G. See Bell, R. P., 1696
Robertson, A. See Cavill, G. W. K., 1544
Sainsbury, G. L. See Green, A. L., 1583
Saville, B. See Green, A. L., 1583
Shaw, K. B. See Bullock, E., 1430
Sheppard, N. See Ebsworth, E. A. V., 1453
Shoppee, C. W., Jenkins, R. H., and Summers, G. H. R., 1657
Short, E. M. See Hunter, R. F., 1561
Slater, C. A. See Howard, G. A., 1460
Sloan, A. D. B. See Galt, R. H. B., 1588
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Thrower, J. See Fear, E. J. P., 1322
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Todd, Sir A. See Griffin, B. E., 1389
Tucker, S. H., 1462
Vaughan, J. See Fischer, A., 1426
Veitch, J. See Fear, E. J. P., 1322
Waddington, T. C., 1708
Wade, K. See Greenwood, N. N., 1663, 1671
Walsh, J. R. See Craig, D. P., 1613
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Watkins, T. I., 1443
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White, T. R. See Cass, R. C., 1406
Whiting, M. C. See Bell, I., 1313
Whitley, A. See Martin, R. L., 1394
Wild, A. M. See Petrow, V., 1508
Willcox, T. J. See Mann, F. G., 1525
Williams, A. A. See Ahrland, S., 1403
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Woodward, L. A., Greenwood, N. N., Hall, J. R., and Worrall, I. J., 1505
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A second carbonyl band in the spectra of hydroxy-esters. By H. B. HENBEST, G. D. MEAKINS, and T. I. WRIGLEY

266. *Researches on Acetylenic Compounds. Part LXI.* The Synthesis of Three Polyacetylenic Esters.*

By Ian Bell, E. R. H. Jones, and M. C. Whiting.

Rational syntheses of three esters of the type (I), which include the first two natural polyacetylenic compounds to be isolated, are described. They

(I) R·C≡C·C≡C·CH=^{cis}CH·CO_2Me (R = Me·CH_2·CH_2, *cis*-Me·CH=CH, and Me·C≡C)

involve oxidative coupling of *cis*-pent-2-en-4-yn-1-ol with the appropriate acetylenic hydrocarbon, followed by cautious oxidation and methylation.

Among natural polyacetylenes two esters (I; R = Me·CH_2·CH_2 and *cis*-Me·CH=CH) occupy a unique position, in that they were, by a wide margin, the first two to be isolated and given structural formulæ,[1,2] and are the most widely distributed compounds in this class. Their structures are known through degradative studies, and have been confirmed by the total synthesis of the corresponding Δ^2-*trans*-isomers, obtained from them by photoisomerisation.[3,4] A third member of the series, the ester (I; R = Me·C≡C), is much less frequently encountered, but is present in *Artemesia vulgaris* L.[5] Its constitution has not been rigorously proved, but seemed highly probable on the basis of spectrographic evidence; the two *trans*-isomers, Me·$[C{\equiv}C]_3$·CH=CH·CO_2Me and Me·CH=CH·$[C{\equiv}C]_3$·CO_2Me, have been synthesised [6a-c] and shown to be different.

Of these three esters, the least unsaturated was first isolated from *Lachnophyllum gossypinum* Bge,[1] and has since been found in a large number of *Erigeron* species;[7] ester (I; R = *cis*-Me·CH=CH) was isolated from scentless mayweed[2] [*Tripleurospermum maritimum* (L) Koch, formerly *Matricaria inodora L*], and from numerous *Erigeron* species.[7] They have become known as "lachnophyllum ester" and "matricaria ester," while the ester (I; R = Me·C≡C) has been frequently referred to as "dehydromatricaria ester."

Only one compound (methyl *cis*-hex-2-en-4-ynoate) in which the characteristic grouping *cis*-C≡C·CH=CH·CO_2Me occurs had previously been synthesised;[8] the method used is unlikely to be applicable to the natural esters. The preparation of *cis*-hex-3-en-5-yn-2-ol and *cis*-pent-2-en-4-yn-1-ol[9] suggested a more promising approach. The secondary alcohol is much the more accessible, and was investigated first, the *trans*-isomer being used in model experiments. Oxidation of the mixed isomers of the latter to hex-3-en-5-yn-2-one with chromic acid in acetone had already been reported.[10] Applied to the pure *trans*-isomer,[9] this technique gave a fair yield of a ketonic product, which, however, was difficult to separate from some unchanged alcohol. Applied to *cis*-hex-3-en-5-yn-2-ol[9] it gave a product consisting almost entirely of unchanged starting material, although the chromic acid underwent reduction; evidently a small proportion of the alcohol suffered extensive breakdown. Manganese dioxide oxidation[11] was then investigated, and gave a good yield of a product which crystallised readily. After recrystallisation, *trans*-hex-3-en-5-yn-2-one, m. p. 12·5—13°, had $\varepsilon_{max.}$ 16,500 at 2575 Å, as against $\varepsilon_{max.}$ 11,500 quoted by Bowden

* Part LX, *J.*, 1958, 1054.

[1] Wiljams, Smirnov, and Golmov, *Zhur. obschchei Khim.*, 1935, **5**, 1195.
[2] N. A. Sørensen and Stene, *Annalen*, 1941, **549**, 80.
[3] Bruun, Haug, and N. A. Sørensen, *Acta Chem. Scand.*, 1950, **4**, 850.
[4] Bruun, Christensen, Haug, J. S. and N. A. Sørensen, *ibid.*, 1951, **5**, 1244.
[5] Stavholt and N. A. Sørensen, *ibid.*, 1950, **4**, 1567.
[6] (*a*) Christensen and N. A. Sørensen, *ibid.*, 1952, **6**, 602; (*b*) J. S. Sørensen, Bruun, Holme, and N. A. Sørensen, *ibid.*, 1954, **8**, 26; (*c*) Bohlmann and Mannhardt, *Chem. Ber.*, 1955, **88**, 428.
[7] Tronvold, Nestvold, Holme, J. S. and N. A. Sørensen, *Acta Chem. Scand.*, 1953, **7**, 1375.
[8] Allan, Jones, and Whiting, *J.*, 1955, 1862.
[9] Bell, Jones, and Whiting, *J.*, 1957, 2597.
[10] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39.
[11] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.

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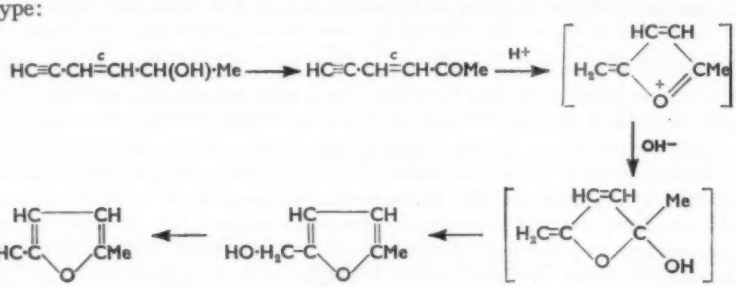
et al.;[10] evidently the specimen obtained earlier was a mixture of the ketone with up to 30% of the *cis*- and *trans*-alcohol. Oxidative cross-coupling with pent-1-yne gave *trans*-undec-3-ene-5 : 7-diyn-2-one, which underwent hypochlorite oxidation in methanol to give the *trans*-isomer of " lachnophyllum acid " (IV; R = Me·CH_2·CH_2) in 80% yield.

Manganese dioxide oxidation of *cis*-hex-3-en-5-yn-2-ol was now investigated, and was at once found to be much slower than that of the *trans*-form. It could be followed by the development of absorption at *ca.* 2600 Å, but the product always consisted of the desired ketone, starting-material, and a higher-boiling product. The last was isolated, and identified as 5-methylfurfuraldehyde, formed presumably by a reaction sequence of the annexed type:



The *cis*-ketone was readily identified by infrared bands at 1671 and at 769 and 753 cm.$^{-1}$, and the relatively weak absorption near 960 cm.$^{-1}$. Considerable difficulty, however, was encountered in purifying it, and results appeared to depend upon the state of the active manganese dioxide used; yields ranged from 20% downwards. A 2 : 4-dinitrophenylhydrazone was readily obtained, markedly different from that of the *trans*-ketone.[10]

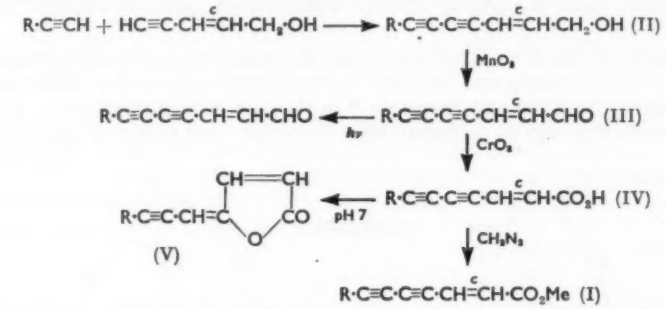
Unfortunately, oxidative coupling of the *cis*-hex-3-en-5-yn-2-one with pent-1-yne gave, instead of the expected ketone, a product, m. p. 40°, which showed no C=O stretching band in the infrared spectrum, and had a single intense absorption maximum at 3320 Å. It had clearly been formed by some cyclisation related to that leading to 5-methylfurfuraldehyde. Hypochlorite oxidation of the C_6 ketone gave a moderate yield of pent-2-en-4-ynoic acid, but the *trans*-isomer predominated in the crude product, according to infrared results.

Because of the difficulties being encountered with *cis*-hexenynol, concurrent investigations on the use of *cis*-pent-2-en-4-yn-1-ol were begun. In the *trans*-series oxidation with manganese dioxide gave *trans*-pent-2-en-4-ynal, m. p. 18·5—19° (previously prepared in a crude state by Sondheimer [12] and by Bohlmann and Viehe [13]) and oxidative coupling with pent-1-yne led to *trans*-dec-2-ene-4 : 6-diynal. Oxidation to the *trans*-C_{10} acid with silver oxide proceeded smoothly. In the *cis*-series, however, oxidation of pent-2-en-4-yn-1-ol with chromic acid gave a mixture of *trans*-pent-2-en-4-ynoic acid and a liquid with vesicant properties; this was probably protoanemonin, formed by a cyclisation of the type discussed below. It seemed unlikely that *cis*-pent-2-en-4-ynal would be easily isolable, and the crossed-coupling reaction was therefore carried out first: *cis*-dec-2-ene-4 : 6-diyn-1-ol (II; R = Me·CH_2·CH_2) was readily obtained. Again, however, chromic acid oxidation gave only a very low yield of acidic material, without the expected ultraviolet absorption spectrum, and thus no doubt obtained by fission. Manganese dioxide oxidation, on the other hand, gave a 90% yield of the *cis*-aldehyde (III; R = Me·CH_2·CH_2). This showed no strong tendency either to isomerise to the *trans*-form or to cyclise, but on treatment with silver oxide it gave only the *trans*-acid, despite the exclusion of bright light. Molecular oxygen in the presence of manganese acetate [14] had no effect after 5 days. Finally the aldehyde was oxidised with chromic–sulphuric acid (1 equivalent) and the desired *cis*-acid

[12] Sondheimer, Ph.D. Thesis, London, 1948.
[13] Bohlmann and Viehe, *Chem. Ber.*, 1955, **88**, 1347.
[14] Owen, *J.*, 1943, 463.

was obtained in about 25% yield. Methylation with diazomethane gave the corresponding ester, identical with the natural product kindly supplied by Professor Sørensen.

It is remarkable that *cis*-αβ-ethylenic γδ-acetylenic alcohols, whether primary or secondary, are so much less readily oxidised by chromic acid than the corresponding *trans*-forms. Possibly the use of manganese dioxide is successful because of an effectively small steric requirement in the removal of an α-proton by a centre of oxidative power adjacent to the site of adsorption. The use of manganese dioxide in a preliminary oxidation to the aldehyde stage may be generally useful in the process $R{\cdot}CH_2{\cdot}OH \longrightarrow R{\cdot}CO_2H$, since direct treatment of the alcohol with chromic acid usually results in the formation of appreciable quantities of the ester, $R{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}R$.



Once the method had been worked out for the ester (I; R = Pr^n) it was applied to the other two esters; in these cases the two primary alcohols were obtained without difficulty, but the aldehydes (no doubt because they absorbed at longer wavelengths) were much more sensitive to photo-stereomutation. In each case it was preferable to use much more than one equivalent of chromic acid in the second stage. The triacetylenic acid was obtained, after the usual bicarbonate separation, as a mixture with a much larger quantity of a γ-lactonic impurity (V; R = Me·C≡C) characterised by an intense band at 1788 $cm.^{-1}$. (Similar contaminants were encountered in the other cases, but not in such large quantity.)

TABLE 1. *C=O stretching and C–H deformation frequencies ($cm.^{-1}$) in carbon disulphide.*

Compound		ν(C=O) (ε)		ν(C–H) (ε)	
HC≡C·CH=CH·CHO	*trans*	1689 (175)		955 (120)	
HC≡C·CH=CH·CO·Me	*trans*	1697 (140) ‡	1680 (170) ‡	957 (170)	[780 (40)]
	cis	1671 (190)		[958 (20)]	769 (40) *
$C_3H_7{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CO{\cdot}Me$	*trans*	1691 (210)	1676 (240)	952 (200)	
$[C{\equiv}C{\cdot}CH{=}CH{\cdot}CO{\cdot}Me]_2$	*trans*	1692 (280)	1675 (330) §		
$C_3H_7{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CHO$	*trans*	1688 (350)		948 (180)	
	cis	1678 (300)			757 (130)
$CH_3{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CHO$	*trans*	1682 (400)		949 (120)	
	cis	1677 (300)			753 (100)
$C_3H_7{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CO_2H$	*trans*	1684 (450)		953 (200)	
	cis	1690 (320)			816 (85)
$CH_3{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CO_2H$	*(cis)*	1695 (400)			816 (85) †
$CH_3{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CO_2H$	*(cis)*	1680 (s)			818 (m.)
$C_3H_7{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CO_2Me$	*(cis)*	1730 (270)	1715 (240)		809 (150)
$CH_3{\cdot}CH{=}CH{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CO_2Me$	*(cis)*	1728 (210)	1716 (220)		808 (145) †
$CH_3{\cdot}[C{\equiv}C]_2{\cdot}CH{=}CH{\cdot}CO_2Me$	*(cis)*	1725 (260)	1712 (280)		806 (145)

* A band at 753 $cm.^{-1}$ is also present.
† Plus a band at ~720 $cm.^{-1}$ attributable to $cis\text{-}CH_3{\cdot}CH_2{\cdot}CH{=}CH{\cdot}C{\equiv}C{\cdot}$.
‡ The relative intensities of these two bands were unchanged in carbon tetrachloride or in chloroform. § In CCl_4.

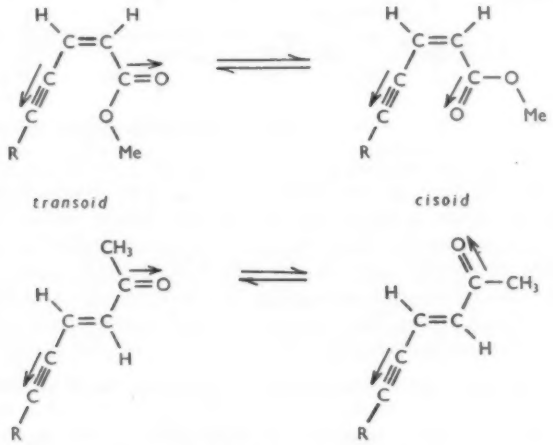
After various attempts to separate the acid from this lactone had failed, it was realised that the lactone was not formed in the chromic acid oxidation process, but rather in the separation of the acidic fraction; and when this step was omitted, the essentially pure triacetylenic *cis*-acid was obtained. It was then shown to undergo rapid cyclisation to the

lactone, isolated as a crystalline solid, in neutral aqueous solution at room temperature. This reaction is discussed at greater length by Christensen, Sørensen, and the present authors,[15] who also report the identity of " Composit-cumulene " [16] with the corresponding lactone (V; R = *cis*-Me·CH=CH).

Methylation of the two *cis*-acids gave the methyl esters, identical with the naturally occurring compounds.

Infrared Absorption Spectra.—The spectra of most of the compounds discussed above were determined, and the more important results are summarised in Table 1. Conditions approximated to those of Part L,[17] but the intensities are generally lower than those reported in the previous paper by about 30%, presumably owing to cell path-length inaccuracy and/or lower resolution. Except where stated, carbon disulphide was used as solvent.

The splitting of the C=O stretching band in unsaturated carbonyl compounds was discovered by Allan, Meakins, and Whiting,[17] in the case of esters *cis*-R·C≡C·CH=CH·CO_2Me, and independently by Allen and Bernstein [18] in the case of furfuraldehyde. Both groups explained the effect as due to conformational isomerism, and this now appears to be well



established.[19] The present results modify the situation in that they show that dipole interactions, such as must occur with the esters of type (I), are not responsible for the different frequencies of the *cisoid* and *transoid* forms.

Whereas in the esters the C–C≡C and C=O dipoles are at 120° and 0° in the *transoid* and *cisoid* forms, respectively, in the two forms of *trans*-hex-3-en-5-yn-2-one they are both at 120°. Yet this ketone also shows two bands, of comparable intensity, and separated by about the same frequency difference; evidently the two different frequencies of the conformational isomers are a direct consequence of the relative orientation of the C=C and C=O bonds. As was observed for the *cis*-esters, changes in the rest of the molecule do not appreciably affect the carbonyl bands. In substances R·C≡C·CH=CH·COX, this phenomenon is observed in the *cis*-esters, but not the *trans*-; in the *trans*-ketones, but not the *cis*-; and in neither of the aldehydes. The last fact is readily intelligible, since the second condition for its observation is that the two conformational isomers should be present in comparable

[15] Christensen, N. A. Sørensen, Bell, Jones, and Whiting, " Festschrift Arthur Stoll," Basel, 1957, p. 545; see also Christensen, *Acta Chem. Scand.*, 1957, **11**, 572.
[16] Sørensen and Stavholt, *Acta Chem. Scand.*, 1950, **4**, 1080.
[17] Allan, Meakins, and Whiting, *J.*, 1955, 1874.
[18] Allen and Bernstein, *Canad. J. Chem.*, 1955, **33**, 1055.
[19] R. N. Jones, Forbes, and Mueller, *ibid.*, 1957, **35**, 504; Cromwell, Abs. Paper, 131st Meeting, Amer. Chem. Soc., April 1957 (p. 82-o).

quantity, and in the aldehydes (*cis* or *trans*), as distinct from the esters and ketones, there is a considerable steric advantage for the *transoid* forms, which are thus probably present in large excess.

TABLE 2. *Ultraviolet absorption spectra of* C_5 *and* C_6 *intermediates.*

		Å	
trans-Pent-2-en-4-ynal	(alcohol)	Max., 2575 (ε 18,000) [a]	
	(hexane)	Max., 2455 (ε 21,000)	Min., 2530 (ε 17,500)
		Max., 2575 (ε 20,500)	
trans-Hex-3-en-5-yn-2-one	(alcohol)	Max., 2575 (ε 16,500) [b]	Min., 3030 (ε 38)
		Max., 3300 (ε 56)	
cis-Hex-3-en-5-yn-2-one	(alcohol)	Max., 2560 (ε 10,500)	

[a] For a crude specimen (no refractive index, m. p., or analytical data), Bohlmann and Viehe (*Chem. Ber.*, 1955, **88**, 1347) give $\lambda_{max.}$ 2570 A, ε 10,800 in methanol. [b] For a specimen obtained from the mixed isomers of hex-3-en-5-yn-2-ol and chromic acid, Bowden, Heilbron, Jones, and Weedon (*J.*, 1946, 39) give $\lambda_{max.}$ 2550 Å, ε 11,500.

In the acetylenic αβ-ethylenic aldehydes and ketones a *cis*-ethylenic linkage displaces the carbonyl band further to lower frequency than a *trans*-bond, in contrast to the results for esters.[17] The C–H out-of-plane deformation frequencies amplify the earlier results.[17]

Ultraviolet Absorption Spectra.—Data for the simple intermediates are compared, in Table 2, with each other and with earlier values.

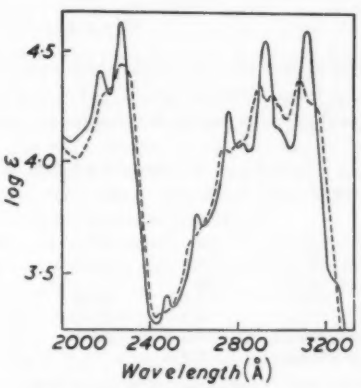


FIG. 1. ——— *Dec-2-ene-4 : 6-diynal (in hexane).*
– – – – *Undec-3-ene-5 : 7-diyn-2-one (in hexane).*

The spectra of *trans*-dec-2-en-4 : 6-diynal (IV) and of the corresponding methyl ketone are of especial interest and are illustrated (Fig. 1). Broadly, they are typical of diacetylenes with one or two ethylenic or carbonyl-containing end-groups; that is, two series of bands are present, one beginning at ~3100 Å (*A*,*B* ··· bands), one at about 2300 Å (*L*,*M* ··· bands), each group spaced at about 2000 cm.$^{-1}$. In the ketone, however, the bands of the *A* group are each doubled, as though two components were present, one absorbing at about 50 Å longer than the other, and present in rather smaller concentration or having a rather smaller extinction coefficient. The aldehyde, on the other hand, shows at first sight a normal spectrum; yet minor maxima and inflexions are present which suggest that a second component, absorbing at longer wavelengths, is present in much smaller quantity than the main component. The *L*-band groups reveal a similar, if less pronounced, effect. Clearly these effects can be correlated with the infrared evidence for the presence of two conformational isomers in comparable quantities for the ketone, but in very unequal quantities for the aldehyde. This may be true quite generally for ethylenic carbonyl compounds, but the majority have ultraviolet absorption spectra so devoid of vibrational fine structure, even in non-polar solvents, that the superposition of two similar spectra separated by a small interval is not detectable. If the C=O stretching frequencies also differed very little, the phenomenon would be difficult to observe.

Table 3 lists the spectra of the various C_{10} intermediates and by-products which have not already been reported by the Trondheim school, with whose results our other data are in good agreement. Fig. 2 illustrates the absorption spectra of the 2 : 4-dinitrophenylhydrazones of the *cis*- and *trans*-aldehydes (III), which show, in a remarkably clear case,

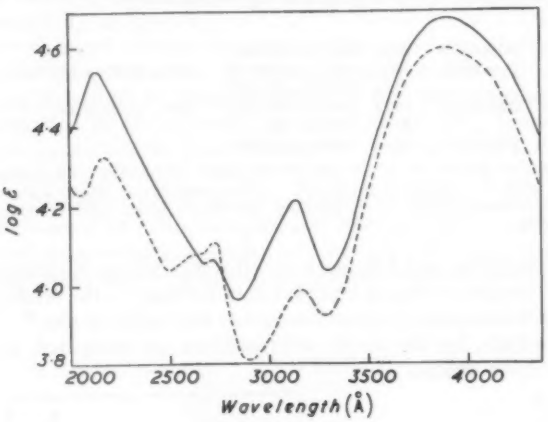


FIG. 2. 2 : 4-*Dinitrophenylhydrazone of* trans(———) *and* cis(– – – –)-*dec-2-ene-4* : 6-*diynal, in alcohol.*

N.B. Hex-1-en-3 : 5-diyne has absorption maxima at 2770, 2620, 2480, and 2360 Å, respectively, with ε values of the order of 10^3—10^4 ¶(Cook, Jones, and Whiting, unpublished work).

the appearance of bands attributable to a partial chromophore (–C≡C·C≡C·CH=CH–) when the linear *trans*-C≡C·C≡C·CH=CH·CH=N·NH·$C_6H_3(NO_2)_2$ system is replaced by the bent (and perhaps partly non-coplanar) *cis*-analogue.

TABLE 3. *Ultraviolet spectra of* C_{10} *intermediates and symmetrical by-products.*

Max. (Å)	$10^{-3}\varepsilon$	Min. (Å)	$10^{-3}\varepsilon$	Max. (Å)	$10^{-3}\varepsilon$	Min. (Å)	$10^{-3}\varepsilon$
(*cis*-HO·CH_2·CH=CH·C≡C·)$_2$				*cis* : *cis*-CH_3·CH=CH·[C≡C]$_2$·CH=CH·CH_2·OH			
2310	28	2330	27·5	2180	26·5	2215	26
2375	29	2435	21	2370	30	2435	22
2470	24	—	—	2465	24	2560	3·5
2625	7·4	2700	4·4	2625	7·4	2705	4·5
2775	14·5	2860	5·5	2775	14	2870	5·5
2945	22·5	3050	4·5	2945	21·5	3055	4·4
3135	18·5			3140	18		
(*trans*-Me·CO·CH=CH·C≡C·)$_2$				*cis*-C_3H_7·[C≡C]$_2$·CH=CH·CH_2·OH			
2235	25	2345	16	2300	2·5	2225	1·8
2780	27·5	2960	16·5	2415	5·2	2340	1·6
3060	20·5	3140	18·5	2540	11·5	2460	2·8
3260	26·5	3385	18·0	2685	19	2610	4·0
3490	23·5			2845	15·5	2770	3·2
				cis-C_3H_7·[C≡C]$_2$·CH=CH·CHO			
				2205	15	2075	8
				2295	20	2245	12
				2485	1·9	2450	1·7
				2780	10	2505	1·8
				2835	8·9	2820	8·5
				2950	21	2870	8·0
				3140	23	3060	8·0

EXPERIMENTAL

General techniques for manipulating low-melting, unstable substances were described in Part XLIX of this Series.[8] It was, however, necessary also to exclude light as completely as possible from all operations when polyacetylenic *cis*-αβ-ethylenic aldehydes, esters, and acids were handled, since these showed a tendency to isomerise to the *trans*-isomers.

Manganese dioxide was prepared by the method of Attenburrow *et al.*[11] and was washed by decantation for several days. Thorough washing was essential for high activity; after final washings with methanol and ether the oxide was dried overnight at 100°.

Silver oxide was precipitated from aqueous solution, washed with water, methanol, and ether, and dried at 20°/10 mm.

Light petroleum refers to the fraction of b. p. 60—80°. Ultraviolet and infrared spectra were determined with a Unicam S.P. 500 and a Perkin-Elmer 21 Spectrophotometer, respectively, the solvents being alcohol, and carbon disulphide, unless otherwise stated.

trans-*Hex*-3-*en*-5-*yn*-2-*one*.—*trans*-Hex-3-en-5-yn-2-ol [9] (4·8 g.), active manganese dioxide (48 g.), and methylene dichloride (400 c.c.) were shaken together for 2 hr. at 18°, the reaction being followed by the increasing absorption-intensity at *ca.* 2600 Å, and diminishing intensity at *ca.* 2200 Å. When no further change was observed (variable, but usually 2—24 hr.) the manganese dioxide was filtered off and washed with hot methylene dichloride. Removal of the solvent through a Dufton column and distillation of the residue gave the essentially pure *ketone* (3·3 g., 70%), b. p. 60°/20 mm., which solidified at 0°. Three crystallisations from pentane gave needles, m. p. 12·5—13°, n_D^{20} 1·4990 (Found: C, 76·85; H, 6·8. C_6H_6O requires C, 76·55; H, 6·45%). (For their specimen of hex-3-en-5-yn-2-one Bowden *et al.*[10] give b. p. 60—63°/20 mm., n_D^{16} 1·4954.) The 2 : 4-dinitrophenylhydrazone had m. p. 182° (decomp.) [lit., m. p. 181° (decomp.)].

Oxidation of cis-*Hex*-3-*en*-5-*yn*-2-*ol*.—The alcohol [9] (9·6 g.), manganese dioxide (96 g.), and methylene dichloride (800 c.c.) were shaken at 20° for 100 hr. After filtration and thorough washing of the residue, the solvent was removed and the residual liquid was distilled, giving the crude *cis*-ketone (1·9 g.), b. p. 48—54°/14 mm., n_D^{20} 1·4966—1·5000, and 5-methylfurfuraldehyde (1·1 g.), b. p. 66°/14 mm., n_D^{20} 1·5264. Careful redistillation gave cis-*hex*-3-*en*-5-*yn*-2-*one*, n_D^{20} 1·4930 (3 fractions) (Found: C, 76·5; H, 6·85%), and the aldehyde, n_D^{25} 1·5270 (Found: C, 65·4; H, 5·7. Calc. for $C_6H_6O_2$: C, 65·45; H, 5·5%). Light absorption: max. 2250 and 2835 Å; min., 2100 and 2415 Å (10^{-3} ε 2·8, 17, 1·8, 0·9, respectively). For the aldehyde Rinkes [20] gives b. p. 83—85°/15 mm.

The 2 : 4-*dinitrophenylhydrazone* of the *cis*-ketone formed orange-red plates, m. p. 152—153°, from ethanol (Found: C, 52·45; H, 3·7. $C_{12}H_{10}O_4N_4$ requires C, 52·55; H, 3·7%). The 2 : 4-*dinitrophenylhydrazone* of 5-methylfurfuraldehyde separated from ethanol in red needles, m. p. 211·5—213·5° (Found: C, 49·9; H, 4·1. $C_{12}H_{10}O_5N_4$ requires C, 49·65; H, 3·5%), and had light absorption max. 2200, 2640, 3000, and 3830 Å, min. 2110, 2410, 2880, and 3210 Å (10^{-3} ε 16, 19·5, 8·8, 16, 28·5, 15, 13·5, 8, and 5·3, respectively).

5-Methylfuroic Acid.—5-Methylfurfuraldehyde (100 mg.), obtained as above, freshly precipitated silver oxide (500 mg.), and methanol (10 c.c.) were shaken together for 18 hr. at 20°. Isolation of the acidic fraction with ether gave the acid (91 mg.), m. p. 108·5—109·5° after crystallisation from light petroleum (Hill and Sawyer [21] gave m. p. 108—109°).

trans-*Pent*-2-*en*-4-*ynal*.—*trans*-Pent-2-en-4-yn-1-ol (4·1 g.), manganese dioxide (41 g.), and methylene dichloride (350 c.c.) were shaken at 20° for 8 hr.; light-absorption data then indicated complete reaction. The manganese dioxide was filtered off and washed well. Removal of solvent and distillation of the residue gave the aldehyde (1·7 g., 43%), b. p. 61—62°/54 mm., $n_D^{21\cdot5}$ 1·5128—1·5132, m. p. 17°. Crystallisation from pentane gave long needles, m. p. 18·5—19°, which gave the expected ultraviolet and infrared spectra but were too unstable to yield satisfactory analytical data (Sondheimer [13] gives b. p. 82—84°/135 mm., n_D^{20} 1·5030). The 2 : 4-*dinitrophenylhydrazone* formed brown-red needles from ethanol which decomposed above 150° without melting, as stated by Bohlmann and Viehe [13] (Found: C, 51·2; H, 3·5. $C_{11}H_8O_4N_4$ requires C, 50·8; H, 3·1%).

trans-*Dec*-2-*ene*-4 : 6-*diynal*.—The above aldehyde (1·4 g.) and pent-1-yne (5·1 g.) were mixed and added to a stirred suspension of cuprous chloride (23·5 g.) and ammonium chloride (37 g.) in water (120 c.c.), which had been brought to pH 3 by addition of a little concentrated hydrochloric acid. After 15 min. the mixture was cooled to 0°, while hydrogen peroxide ("100-vol."; 50 c.c.) was added slowly below the liquid surface, at such a rate that the temperature did not rise above 10° (2 hr.), the mixture becoming bright green. After a further hour at 5°, phosphoric acid (10%; 200 c.c.) was added and the neutral product was isolated with ether (no appreciable acidic fraction was obtained). Light petroleum was added to the residue, and the insoluble *trans* : *trans*-deca-2 : 8-diene-4 : 6-diynedial (390 mg.), m. p. 135—140°, was removed [Weedon [22] gives m. p. 144° (decomp.)]. The residue was distilled, to give

[20] Rinkes, *Org. Synth.*, 1934, **14**, 62.
[21] Hill and Sawyer, *Amer. Chem. J.*, 1898, **20**, 171.
[22] Weedon, *J.*, 1954, 4168.

deca-4 : 6-diyne, which was discarded, and essentially pure trans-*dec*-2-*ene*-4 : 6-*diynal* (1·16 g.), b. p. 92—100° (bath-temp.)/0·1 mm., which after redistillation had n_D^{17} 1·6004, m. p. 2—3° (Found: C, 81·75; H, 7·3. $C_{10}H_{10}O$ requires C, 82·15; H, 6·9%). The 2 : 4-*dinitrophenylhydrazone* formed brick-red needles, m. p. 195—196°, from ethanol (Found: C, 58·85; H, 4·45. $C_{16}H_{14}O_4N_4$ requires C, 58·9; H, 4·3%).

trans-*Undec*-3-*ene*-5 : 7-*diyn*-2-*one*.—Oxidative coupling, as above, of *trans*-hex-3-en-5-yn-2-one (3·1 g.) and pent-1-yne (9·2 g.) using cuprous chloride (41·5 g.), ammonium chloride (67 g.), and hydrogen peroxide (" 100-vol.; " 60 c.c.), gave a neutral fraction from which was precipitated trans : trans-*dodeca*-3 : 9-*diene*-5 : 7-*diyne*-2 : 11-*dione* (570 mg.), m. p. 138—138·5° after recrystallisation from benzene–light petroleum (Found: C, 77·2; H, 5·6. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%).

The light petroleum filtrates were evaporated and the residue was distilled, giving decadiyne and the essentially pure ketone (2·6 g.), b. p. 100° (bath-temp.)/0·05 mm. After crystallisation from pentane trans-*undec*-3-*ene*-5 : 7-*diyn*-2-*one* formed thick needles, m. p. 17—17·5°, n_D^{22} 1·5812 (Found: C, 82·6; H, 7·75. $C_{11}H_{12}O$ requires C, 82·45; H, 7·5%). The 2 : 4-*dinitrophenylhydrazone* formed bright red prisms, m. p. 135—135·5°, from ethanol (Found: C, 60·25; H, 4·75. $C_{17}H_{16}O_4N_4$ requires C, 60·0; H, 4·75%).

trans-*Dec*-2-*ene*-4 : 6-*diynoic Acid*.—(*a*) The corresponding aldehyde (500 mg.), silver oxide (1·4 g.), and potassium hydroxide (200 mg.) in methanol (10 c.c.) were shaken at 20° for 24 hr. The acid fraction (290 mg.) was isolated and crystallised from aqueous ethanol (charcoal), giving plates, m. p. 124—125° (Holme and Sørensen [23] give m. p. 123·5—124·5° for the acid prepared from the naturally occurring *trans*-ester).

(*b*) The corresponding methyl ketone (320 mg.) in methanol (90 c.c.) and water (7·5 c.c.) was treated with 4·4N-sodium hypochlorite (2·5 c.c.). The reaction was followed spectroscopically, and was almost complete in 3 hr. at 20°. Isolation of the acidic fraction (260 mg.; m. p. 116—122°) and crystallisation from light petroleum gave needles, m. p. and mixed m. p. 124—125°.

cis-*Dec*-2-*ene*-4 : 6-*diyn*-1-*ol*.—A mixture of *cis*-pent-2-en-4-yn-1-ol (1·0 g.) pent-1-yne (6·4 g.), cuprous chloride (27 g.), ammonium chloride (43 g.), and water (150 c.c.) was treated with hydrogen peroxide (" 100-vol.; " 40 c.c.). Isolation of the product with ether and removal of the solvent left a residue which was extracted with warm pentane (10 × 100 c.c.); the insoluble residue (146 mg.; m. p. 45—46°) crystallised from ether–pentane, giving cis : cis-*deca*-2 : 8-*diene*-4 : 6-*diyne*-1 : 8-*diol*, m. p. 62—63° (Found: C, 74·15; H, 6·3. $C_{10}H_{10}O_2$ requires C, 74·05; H, 6·2%).

Evaporation of the pentane extracts and distillation of the residue gave much deca-4 : 6-diyne, b. p. 65—75° (bath-temp.)/0·4 mm., which was discarded, and cis-*dec*-2-*ene*-4 : 6-*diyn*-1-*ol* (970 mg.), b. p. 121—126° (bath-temp.)/0·4 mm., n_D^{17} 1·5630 (Found: C, 81·4; H, 8·3. $C_{10}H_{12}O$ requires C, 81·05; H, 8·15%). The 3 : 5-*dinitrobenzoate*, prepared by the method of Mills,[24] formed needles, m. p. 91—92° (Found: C, 59·75; H, 4·3. $C_{17}H_{14}O_6N_2$ requires C, 59·65; H, 4·1%).

cis-*Dec*-2-*ene*-4 : 6-*diynoic Acid*.—*cis*-Dec-2-ene-4 : 6-diyn-1-ol (105 mg.) and active manganese dioxide (1·0 g.) in methylene chloride (15 c.c.) were stirred rapidly at room temperature. The reaction was followed spectroscopically and was complete in 2 hr. The manganese dioxide was filtered off and thoroughly washed with boiling solvent. Evaporation left the *cis*-aldehyde (93 mg.) which in another experiment was purified by chromatography and obtained as a light yellow oil, n_D^{19} 1·5780, characterised by its ultraviolet and infrared spectra and as its 2 : 4-*dinitrophenylhydrazone*, which formed fine red needles, m. p. 112—113° (Found: C, 58·75; H, 4·45. $C_{16}H_{14}O_4N_4$ requires C, 58·9; H, 4·3%).

The aldehyde was dissolved in pure acetone (15 c.c.), and the solution was stirred rapidly at −5° while a solution of chromic acid (6N in 12N-sulphuric acid; 0·22 c.c.) was added, one micro-drop at a time, from a capilliary pipette during 30 min. Stirring at −5° was maintained for 1 hr., the mixture becoming green. Water (40 c.c.) was added, and the mixture was extracted with ether; the extracts were washed with saturated aqueous potassium hydrogen carbonate solution. After drying ($MgSO_4$), the ether solution was evaporated to give recovered aldehyde (51 mg.), shown by its ultraviolet and infrared spectra to be essentially pure. The bicarbonate extracts were cautiously acidified with 2N-sulphuric acid in the presence of ether; the dried extract was evaporated, giving a semi-solid residue (38 mg.) which could not be purified

[23] Holme and Sørensen, *Acta Chem. Scand.*, 1954, **8**, 280.
[24] Mills, *J.*, 1951, 2332.

by crystallisation. This was dissolved in ether (40 c.c.) and extracted with a solution of potassium hydrogen carbonate (6 mg.) in water (10 c.c.); evaporation of the ether now gave a solid residue (30 mg.; m. p. 59—65°) which crystallised from pentane at low temperatures, then at 20° from light petroleum (b. p. 60—80°), to give the acid as prisms, m. p. 72—74°. Further crystallisation, however, gave fine needles, m. p. 59—60°, evidently a polymorphic form (Found: C, 73·55; H, 6·4. Calc. for $C_{10}H_{10}O_2$: C, 74·05; H, 6·2%). Holme and Sørensen [23] give m. p. 72—73° (indistinct) for the acid prepared from the natural ester.

Methyl cis-*Dec*-2-*ene*-4 : 6-*diynoate* (" *Lachnophyllum Ester* ").—The above acid (30 mg.) in dry ether (10 c.c.) was treated with the theoretical quantity of dry ethereal diazomethane and kept at 17° for 20 min. in the dark. The solution was evaporated to dryness, ether (40 c.c.) was added and, after being washed with saturated potassium hydrogen carbonate and dried, the solution was again evaporated. The residue (30 mg.; m. p. 24—30°) was crystallised four times from pentane at −60°, to give the ester (10 mg.) as fine needles, m. p. 31—32°, undepressed on admixture with the natural product (Found: C, 74·65; H, 6·85. Calc. for $C_{11}H_{14}O_2$: C, 74·95; H, 6·85%).

cis : cis-*Deca*-2 : 8-*diene*-4 : 6-*diyn*-1-*ol*.—Oxidative coupling of *cis*-pent-2-en-4-yn-1-ol (500 mg.) and *cis*-pent-2-en-4-yne (4 g.), using cuprous chloride (17·5 g.), ammonium chloride (27·5 g.), water (100 c.c.), and hydrogen peroxide (" 100-vol.; " 20 c.c.) gave, after isolation of the pentane-soluble fraction, a residue which was distilled at 10^{-3} mm. *cis* : *cis*-Deca-2 : 8-diene-4 : 6-diyne had b. p. 47—60° (bath-temp.), n_D^{19} 1·6054, and cis : cis-*deca*-2 : 8-*diene*-4 : 6-*diyn*-1-*ol* (420 mg.), b. p. 112—114° (bath-temp.), n_D^{19} 1·6170—1·6174 (Found: C, 82·05; H, 7·5. $C_{10}H_{10}O$ requires C, 82·15; H, 6·9%).

Methyl cis : cis-*Deca*-2 : 8-*diene*-4 : 6-*diynoate* (" *Matricaria Ester* ").—The above alcohol (42 mg.) was oxidised with manganese dioxide (400 mg.) in methylene dichloride (20 c.c.) for 2 hr. at 17°, giving the crude aldehyde (40 mg.). This was dissolved in acetone (15 c.c.); chromic acid (0·35 c.c.; 6N in 12N-sulphuric acid) was added at 17° during 1 hr. Isolation of the acidic fraction *via* ice-cold saturated potassium hydrogen carbonate solution, then acidification with cooled dilute sulphuric acid in the presence of ether, gave a residue (12 mg.), which was repeatedly crystallised from ether–pentane, to give *cis* : *cis*-deca-2 : 8-diene-4 : 6-diynoic acid (5 mg.), m. p. 96·5—99·5°. Methylation with diazomethane, as above, and chromatography on neutral alumina gave, in the benzene eluate, a residue (4 mg.; m. p. 30—33°); four recrystallisations from pentane at −45° gave the ester (2·8 mg.) as long needles, m. p. 34—35°, undepressed on admixture with the natural ester (Found: C, 75·4; H, 6·0. Calc. for $C_{11}H_{10}O_2$: C, 75·85; H, 5·8%) (Sørensen and Stene [3] give m. p. 37°, but we were unable to raise the m. p. of the natural material above 34—35°; for the derived acid they give m. p. 98—99°).

cis-*Dec*-2-*ene*-4 : 6 : 8-*triyn*-1-*ol*.—*cis*-Pent-2-en-4-yn-1-ol (1·0 g.) and crude penta-1 : 3-diyne [8] (8·0 g.; n_D^{17} 1·481) were coupled oxidatively by means of cuprous chloride (35 g.), ammonium chloride (55 g.), water (100 c.c.) and hydrogen peroxide (" 100-vol.; " 50 c.c.). Isolation of the product and chromatography on active alumina gave much deca-2 : 4 : 6 : 8-tetrayne and (eluted with 10% methanol in ether) the crude alcohol (540 mg.; m. p. 35—40°). After five crystallisations from ether–pentane at −30° the *alcohol* formed plates, m. p. 41—42·5° (Found: C, 83·55; H, 5·75. $C_{10}H_8O$ requires C, 83·3; H, 5·6%). It rapidly became blue in light.

Methyl cis-*Dec*-2-*ene*-4 : 6 : 8-*triynoate*.—The above alcohol (120 mg.) was oxidised with manganese dioxide (1·2 g.) in methylene dichloride (30 c.c.) at 20° for 2 hr. Isolation of the aldehyde gave a solid, m. p. 48—58° (which on another occasion was recrystallised in diffused daylight and suffered isomerisation to the *trans*-form, m. p. 93—106°, as shown by the substitution of a band at 949 cm.$^{-1}$ for that at 743 cm.$^{-1}$). It was dissolved in acetone (25 c.c.) and treated with chromic acid (0·78 c.c.; 6N in 12N-sulphuric acid), added during 1 hr. at 16°. Water was added and the product was isolated with ether, which was removed to leave a brown residue. Crystallisation from ether–pentane gave, after removal of brown polymeric material (17 mg.), the crude acid (74 mg.), m. p. 145° (decomp.).

This acid (45 mg.) was treated with diazomethane, as above. Chromatography and crystallisation from pentane at −35° gave the *ester* (30 mg.; m. p. 111—113°), which after treatment with norite and further crystallisation formed thick pale yellow needles, m. p. 114—115° (Found: C, 77·15; H, 4·7. Calc. for $C_{11}H_8O_2$: C, 76·75; H, 4·7%). A sample of the natural ester had m. p. 114—115°, undepressed on admixture with the synthetic product (Stavholt and Sørensen [5] give m. p. 113°).

XUM

Lactone of 4-Hydroxydeca-2 : 4-diene-6 : 8-diynoic Acid.—The *lactone* was first obtained from the products of several experiments in which *cis*-dec-2-en-4 : 6 : 8-triynal was oxidised with chromic acid and an attempt was made to isolate the acidic fraction *via* potassium hydrogen carbonate solution. It formed plates, m. p. 135—136° (Found: C, 75·9; H, 4·25. $C_{10}H_6O_2$ requires C, 75·95; H, 3·8%).

cis-Dec-2-en-4 : 6 : 8-triynoic acid (5·0 mg.) was added to saturated potassium hydrogen carbonate solution (10 c.c.). After 5 min. at 20° the solution was extracted with ether; the resultant solid (2·8 mg.) had essentially the same infrared spectrum, characterised by sharp and intense bands at 1788, 1330, 1095, 1059, 934, 867, 820, and 757 cm.$^{-1}$, as for the pure lactone.

We thank Prof. N. A. and Mrs. J. S. Sørensen for their repeated assistance, and for isolating for us generous samples of the natural polyacetylenic esters. Infrared spectra were determined under the supervision of Dr. F. B. Strauss.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, October 8th*, 1957.]

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267. *Organic Fluorine Compounds. Part V.* The Instability of Some Sodium 1 : 1-Di-H-perfluoroalkoxides and its Effect on the Yields of Fluoro-ethers.*

By E. J. P. FEAR, J. THROWER, and J. VEITCH.

Sodium 2 : 2 : 2-trifluoroethoxide and 1 : 1-di-*H*-heptafluorobutoxide liberate fluoride ion in ethers and on dry pyrolysis. 1 : 1-Di-*H*-perfluoro-alcohol is also formed in the latter reaction.

Conditions have been established for the preparation of some fluoro-ethers in improved yields.

ALTHOUGH sodium 1 : 1-di-*H*-perfluoroalkoxides have been used for the synthesis of partially-fluorinated ethers,[1,2] yields have only been fair. Further, we have found no reference to the difficulty of isolating fluoroalkoxides free from fluoride ion.

We have shown that condensation of sodium fluoroalkoxides with toluene-*p*-sulphonates of unfluorinated alcohols is not straightforward. Thus, interaction of equivalent amounts of hexamethylene ditoluene-*p*-sulphonate and sodium 1 : 1-di-*H*-heptafluorobutoxide in dioxan at 80° gave the diether (I) and an appreciable amount of the monotoluene-

(I) $C_3F_7{\cdot}CH_2{\cdot}O{\cdot}[CH_2]_6{\cdot}O{\cdot}CH_2{\cdot}C_3F_7$ $\qquad$ $C_3F_7{\cdot}CH_2{\cdot}O{\cdot}[CH_2]_6{\cdot}OTs$ (II)

sulphonate (II). Similar condensation with butyl toluene-*p*-sulphonate and sodium heptafluorobutoxide in diethylene glycol diethyl ether, gave butyl heptafluorobutyl ether in 55—60% yield, and nine unidentified products. Recovery of 13% of sodium as sodium fluoride indicated that the low yields of ethers were caused by loss of alkoxide through elimination of fluoride ion.

Investigation of the breakdown of 1 : 1-di-*H*-perfluoroalkoxides was hampered by difficulty in obtaining them free from fluoride ion. Indeed, pure sodium heptafluoro-butoxide has not been obtained, although slightly contaminated salt was prepared by a rapid reaction with sodium and a large excess of the fluoro-alcohol in ether. Exchanges with sodium methoxide and heptafluorobutanol in methanol or ether, followed by removal of solvents or precipitation with benzene, gave products of unknown composition, free from unfluorinated alcohol but severely contaminated with fluoride ion. Sodium trifluoro-ethoxide is much less susceptible to degradation, and pure material was prepared by the rapid action of sodium on the alcohol in ether.

Elimination of fluoride ion from sodium trifluoroethoxide in dioxan was slow at room

* Part IV, *J.*, 1956, 3199.

[1] Henne and Smook, *J. Amer. Chem. Soc.*, 1950, **72**, 4378.
[2] McBee and Weesner, U.S.P. 2,452,944; *Chem. Abs.*, 1949, **43**, 2219.

temperature but rapid at 100°. Analysis of the precipitate showed that the elimination was limited to 0·66 mole of sodium fluoride per mole of fluoroalkoxide (Table 1).

TABLE 1.

$CF_3 \cdot CH_2 \cdot ONa$ (mmole)	Time (hr.)	Temp. (° c)	Precipitate F, %	Precipitate NaF, %	NaF (mmole)	$NaF/CF_3 \cdot CH_2 \cdot ONa$ (mol.)
4·48	24	50	15·2	33·6	1·90	0·42
4·28	5	100	14·5	32·1	0·51	0·12
4·14	24	100	20·2	44·6	2·66	0·64
4·69	70	100	20·9	46·2	3·09	0·66
4·43 *	{1 2·5	120} 140}	20·1	44·4	2·18	0·49

* In diethylene glycol diethyl ether.

Degradation of solid sodium trifluoroethoxide was violent at about 180° at atmospheric pressure under nitrogen, with formation of carbon and liberation of fluoride ion. Pyrolysis of sodium trifluoroethoxide and of sodium heptafluorobutoxide *in vacuo* at 140—150° gave the corresponding fluoro-alcohols, and equimolar quantities of sodium fluoride. The amount of heptafluorobutanol formed was 47% of the weight of alkoxide pyrolysed.

Formation of fluoro-alcohol during breakdown of the solid is remarkable. The reaction can best be represented by a disproportionation according to the formal equation:

$$2R_f \cdot CH_2 \cdot ONa \longrightarrow R_f \cdot CH_2 \cdot OH + R_f \cdot CH(Na) \cdot ONa \quad (III)$$
$$(R_f = \text{perfluoroalkyl})$$

Concurrent formation of sodium fluoride may take place by ejection of fluoride ion (with the sodium) from compounds (III) which are related to the heat-sensitive metal perfluoroalkyls.[3] Thermal breakdown of unfluorinated sodium alkoxides of comparable size takes place at 250—350°, and unlike that of sodium fluoroalkoxides, appears to involve rupture of the alkyl–oxygen bond, yielding sodium hydroxide and unsaturated hydrocarbons.[4] The presence of the electronegative perfluoroalkyl group is reflected in the relative volatility and easy solubility in ethers of these sodium 1 : 1-di-*H*-perfluoroalkoxides. Their solubility is not inconsistent with the distribution, by induction, of the source of a high electric field on the fluoroalkoxide anion, and with the likely solvation of the sodium cation. Inductive effects may also explain the lability of the hydrogen atoms, the weakness of the oxygen–sodium link, and hence the low temperature of breakdown to yield fluoro-alcohol.

The easy elimination of fluoride ion in ethers, with formation of some sodium fluoride, may be accounted for by unimolecular (1) or bimolecular (2) ejection of fluoride ion, *e.g.*,

(1) $CF_3 \cdot CH_2 \cdot O^- + CF_3 \cdot CH_2 \cdot ONa \rightleftharpoons CF_3 \cdot CH_2 \cdot OH + CF_3 \cdot \bar{C}H \cdot ONa$

$CF_3 \cdot \bar{C}H \cdot ONa \longrightarrow CF_2 \cdot CH \cdot ONa + F^-$

$CF_2 \cdot CH_2 \cdot O^- + CF_2 \cdot CH \cdot ONa \rightleftharpoons CF_3 \cdot CH_2 \cdot OH + CF_2 \cdot \bar{C} \cdot ONa$

$CF_2 \cdot \bar{C} \cdot ONa \longrightarrow CF \vdots C \cdot ONa + F^-$

(2) $CF_3 \cdot CH_2 \cdot O^- + CF_3 \cdot CH_2 \cdot ONa \longrightarrow CF_3 \cdot CH_2 \cdot OH + F^- + CF_2 \cdot CH \cdot ONa$

$CF_3 \cdot CH_2 \cdot O^- + CF_2 \cdot CH \cdot ONa \longrightarrow CF_3 \cdot CH_3 \cdot OH + F^- + CF \vdots C \cdot ONa$

The overall stoicheiometry of both mechanisms is identical, and the ultimate yield of sodium fluoride is 0·66 mol. of alkoxide, in agreement with the value determined experimentally. Alcoholic solutions of the fluoroalkoxides remain free from fluoride ion even at the boiling point, as do aqueous alkaline (5N) solutions of trifluoroethanol and heptafluorobutanol. This dependence of fluoride-ion elimination on solvent can be interpreted in terms of the equilibrium shown in scheme (1). In presence of excess of an alcohol or water, carbanion formation would be effectively suppressed.

The reaction of sodium fluoroalkoxides with unfluorinated toluenesulphonates in ethers is faster than that of breakdown, and provided the sodium salt is prepared rapidly

[3] Musgrave, *Quart. Reviews*, 1954, **8**, 344.
[4] Durand, *Compt. rend.*, 1921, **172**, 1504.

and used in excess (25%), good yields of fluoro-ethers can be obtained (Table 3) at 70—90°. The aqueous alkylation described by Faurote *et al.*[5] gave fluoro-ethers in only fair yield. Our failure to prepare diheptafluorobutyl ether from heptafluorobutyl toluene-*p*-sulphonate and sodium heptafluorobutoxide in non-aqueous medium can now be attributed to the accelerated decomposition of the alkoxide at 150—220° as required to activate the fluorinated toluene-*p*-sulphonate.[6] Henne and Smook[1] mentioned bis-2:2:2-trifluoroethyl ether but did not give experimental details.

Experimental

1 : 6-*Bis*-(1 : 1-*di*-H-*heptafluorobutoxy*)*hexane* (I).—1 : 1-Di-*H*-heptafluorobutanol (22·0 g., 0·11 mole) in dioxan (100 ml.) was treated with sodium (2·3 g., 0·1 mole), and the reaction completed at 60—70° for 5·5 hr. 1 : 6-Ditoluene-*p*-sulphonyloxyhexane (21·3 g., 0·05 mole; Table 2) was added at 50°. The stirred mixture was heated at 80° for 22 hr., and then cooled, and the precipitate was filtered off, washed thoroughly with dioxan, and dried (15·0 g.) at 110° (theoretical weight of sodium toluene-*p*-sulphonate, 19·4 g.). Excess of dioxan was removed from the filtrate by distillation *in vacuo* (b. p. 16—20°/15 mm.). The residue was treated with water, the lower layer extracted with ether, and the extract dried ($CaSO_4$). Evaporation and then distillation *in vacuo* gave: (i) essentially the desired ether (10·1 g.; 42%); and (ii) a residue (9·7 g.) of much higher boiling point. Redistillation of (i) gave pure 1 : 6-*bis*-(1 : 1-*di*-H-*heptafluorobutoxy*)*hexane*, b. p. 91°/1·4 mm., n_D^{20} 1·3395 (Found: C, 35·1; H, 3·4; F, 55·2. $C_{14}H_{16}O_2F_{14}$ requires C, 34·9; H, 3·4; F, 55·15%).

Distillation of residue (ii) gave 6-(1 : 1-*di*-H-*heptafluorobutoxy*)*hexyl toluene*-p-*sulphonate* (II) (7·2 g.), b. p. 166—169°/0·01 mm., n_D^{20} 1·4410 [Found: C, 45·4; H, 5·0; F, 29·0%; *M* (cryoscopically in benzene), 466. $C_{17}H_{21}O_4SF_7$ requires C, 44·9; H, 4·65; F, 29·3%; *M*, 454].

Butyl 1 : 1-*Di*-H-*heptafluorobutyl Ether*.—1 : 1-Di-*H*-heptafluorobutanol (36·2 g., 0·181 mole) was added dropwise during 1 hr. to finely divided sodium (3·45 g., 0·15 mole) in diethylene glycol diethyl ether (200 ml.); after 1·5 hr. fluoride ion was detected. *n*-Butyl toluene-*p*-sulphonate was then added, the mixture stirred and heated at 80° for 2 hr., and liquid (73 g.), b. p. 88—183°, distilled off. The remaining solid was washed with ether and dried (26·0 g.) at 110° [Found: F, 1·5% ≡ 0·84 g. of NaF (theoretical weight of sodium toluene-*p*-sulphonate, 28·8 g.)]. Fractionation of the distillate through a 1 ft. column (Dixon gauze cylinders, 1/16 × 1/16 in.) gave fractions: (i) (1·5 g.), b. p. 60—93°; (ii) impure heptafluorobutanol (6·2 g.), b. p. 93—97°, n_D^{20} 1·303; (iii) (5·0 g.), b. p. 97—114°; (iv) (2·1 g.), b. p. 114—120°; (v) (3·2 g.), b. p. 120—123°; (vi) *butyl* 1 : 1-*di*-H-*heptafluorobutyl ether* (16·5 g., 43%), b. p. 123—125° (mainly 124·5—125°)/770 mm., n_D^{20} 1·3263 (Found: C, 37·5; H, 4·3. $C_8H_{11}OF_7$ requires C, 37·8; H, 4·5%). Gas–liquid chromatography of this ether on dinonyl phthalate–Celite (at 109°; pressure drop 214 mm.; 0·9 l./hr. of nitrogen) gave a single sharp peak. Chromatography of fractions (i)—(v) on the same column showed that (iv) and (v) contained considerable quantities of the fluoro-ether, and also that nine unidentified components, boiling range 60—123°, were present.

In the following experiments, precautions were taken to protect alkoxides from moisture, oxygen, and carbon dioxide. When materials were handled under nitrogen, this was purified and dried. All apparatus was baked-out in nitrogen. Ether was dried by sodium and by distillation from phosphoric oxide. Sodium was cleaned and cut under ether which was then evaporated in a stream of nitrogen.

Sodium 2 : 2 : 2-*Trifluoroethoxide*.—Sodium (0·992 g., 0·043 mole, weighed under nitrogen) reacted vigorously with 2 : 2 : 2-trifluoroethanol (6·0 g., 0·06 mole; twice distilled from activated calcium sulphate) in dry ether (40 ml.). The ether was then gently distilled off under nitrogen, and the residue dried *in vacuo* (0·05—0·3 mm. of nitrogen) during 18 hr. at 50° (bath) to give *sodium* 2 : 2 : 2-*trifluoroethoxide* (4·67 g., 89%) as a fine white powder (Found: equiv., 123·8. $C_2H_2OF_3Na$ requires equiv., 122). There was no fluoride ion detectable.

Sodium 1 : 1-*Di*-H-*heptafluorobutoxide*.—1 : 1-Di-*H*-heptafluorobutanol (2·980 g., 0·0149 mole) was added rapidly to sodium (0·113 g., 4·92 mmole) under dry ether at room temperature. When the reaction was complete (10 min.), excess of ether and fluoro-alcohol were removed rapidly in a stream of nitrogen at 60—78° (bath). The residue was further dried *in vacuo* ($2·5 \times 10^{-3}$—$1·5 \times 10^{-4}$ mm.) to the theoretical weight during 6 hr. at 50—80° (bath) to give a

[5] Faurote, Henderson, Murphy, O'Rear, and Ravner, *Ind. Eng. Chem.*, 1956, **48**, 445.
[6] Tiers, Brown, and Reid, *J. Amer. Chem. Soc.*, 1953, **75**, 5978.

white wax, essentially sodium 1 : 1-di-*H*-heptafluorobutoxide (1·096 g.) (Found: equiv., 233. Calc. for $C_4H_2OF_7Na$: equiv., 222). It contained some fluoride ion.

Action of Heat on Sodium 2 : 2 : 2-Trifluoroethoxide in Dioxan and in Diethylene Glycol Diethyl Ether.—The solutions of the dry salt in dioxan or diethylene glycol diethyl ether, protected from carbon dioxide and moisture, were heated for the time specified in Table 1, and then cooled. The precipitate was washed with dry ether, dried at 110°, and analysed gravimetrically for fluoride ion.

Effect of Heat on Sodium 2 : 2 : 2-Trifluoroethoxide in vacuo.—Sodium 2 : 2 : 2-trifluoroethoxide (0·660 g., 5·41 mmole) in a flask connected *via* a still-head to a receiver and two traps cooled in liquid nitrogen, was heated in a maintained vacuum (5×10^{-3} mm.). At 100° (bath temp.), material was evolved slowly and collected in the first trap. The temperature was raised and kept at 145—150° for 14·5 hr., and the pressure in the cooled apparatus then restored to atmospheric with nitrogen. During the heating, sodium 2 : 2 : 2-trifluoroethoxide (0·324 g., 49%) (Found: equiv., 123. $C_2H_2OF_3N$ requires equiv., 122), sublimed and 2 : 2 : 2-trifluoroethanol (0·100 g., 1·00 mmole) collected in the first trap. This alcohol, in ether, was chromatographed on dinonyl phthalate–Celite (at 76·5°; 0·95 l./hr. of nitrogen; pressure drop 164 mm.), and gave a single sharp peak which was reinforced on addition of trifluoroethanol. The brown residue in the flask was analysed gravimetrically for fluoride (Found: F, 9·5% ≡ 20·9% NaF; *i.e.* 1·14 mmoles of NaF).

Effect of Heat on Sodium 1 : 1-Di-H-heptafluorobutoxide in vacuo.—The method and apparatus were identical with those described above. Sodium 1 : 1-di-*H*-heptafluorobutoxide (0·687 g., *ca.* 3·1 mmoles) melted at 110—115° (bath)/10^{-2} mm. and volatile material condensed in the first trap. After being heated at 140° for 8 hr., the reaction vessel was cooled and the pressure in the system raise to atmospheric with nitrogen. During the decomposition, a white solid (0·194 g.) (Found: equiv., 357) sublimed and liquid (<5 mg.) condensed in the still-head and receiver. 1 : 1-Di-*H*-heptafluorobutanol (0·287 g., 1·44 mmole) collected in the first trap. The alcohol, in ether, was chromatographed on dinonyl phthalate–Celite (96°; 0·92 l./hr. of nitrogen; pressure drop 202 mm.) and gave three extremely small peaks, followed by a large peak which was reinforced on addition of heptafluorobutanol. The brown residue (0·116 g.) was analysed gravimetrically for fluoride (Found: F, 18·9% ≡ 41·8% NaF, *i.e.* 1·16 mmoles of NaF).

Ditoluene-p-sulphonates of αω-Alkane- and -Oxa-alkane-diols.—These *ditoluene*-p-*sulphonates* (Table 2) were prepared [7] by addition of toluene-*p*-sulphonyl chloride to the alcohol in pyridine.

TABLE 2. *Ditoluene*-p-*sulphonates.*

Compound	Yield (%)	M. p.	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
$TsO\cdot[CH_2]_6\cdot OTs$	91	71—72°	56·6	6·3	56·3	6·15
$TsO\cdot[CH_2]_{10}\cdot OTs$	90	109—109·5	59·8	7·3	59·7	7·1
$TsO\cdot[CH_2\cdot CH_2\cdot O]_2\cdot OTs$	87	81—82	52·6	5·8	52·4	5·7

Preparation of Fluoro-ethers.—The sodium 1 : 1-di-*H*-perfluoroalkoxides (25% excess) were prepared by the rapid action of sodium on the fluoro-alcohols in dioxan. The ditoluene-*p*-sulphonates were then added quickly and the stirred mixtures heated to 80—90°. After 2—5 hr. at this temperature, the mixtures were cooled, sodium toluene-*p*-sulphonate filtered off, and the fluoro-ethers (Table 3) were isolated by the usual methods.

TABLE 3. *Fluoro-ethers.*

Compound	Yield [a] (%)	B. p./mm.	Found (%) C	Found (%) H	Found (%) F	Reqd. (%) C	Reqd. (%) H	Reqd. (%) F
$C_2F_7\cdot CH_2\cdot O\cdot[CH_2]_{10}\cdot O\cdot CH_2\cdot C_2F_7$	78	98—100°/0·18	40·5	4·6	50·1	40·2	4·2	49·4
$C_2F_7\cdot CH_2\cdot O\cdot[CH_2\cdot CH_2\cdot O]_2\cdot CH_2\cdot C_2F_7$	84	92—98/0·2—0·25	32·8	3·2	—	32·7	3·1	—
$CF_3\cdot CH_2\cdot O\cdot[CH_2\cdot CH_2\cdot O]_2\cdot CH_2\cdot CF_3$ ...	75	71—72/0·25	38·4	5·2	—	38·2	5·1	—
$C_2F_7\cdot CH_2\cdot O\cdot[CH_2\cdot CH_2\cdot O]_4\cdot CH_2\cdot C_2F_7$ [b]	66	102—103/0·16	34·5	3·7	47·4	34·4	3·6	47·7

[a] The yields are for ethers having single-peak gas–liquid chromatograms (dinonyl phthalate–Celite). [b] The appropriate ditoluene-*p*-sulphonate was isolated as a very high-boiling syrup (83%).

The authors thank Mr. T. R. F. W. Fennell and his staff for the analyses.

ROYAL AIRCRAFT ESTABLISHMENT, FARNBOROUGH, HANTS. [*Received, August 16th*, 1957.]

[7] (*a*) Marvel and Sekera, *Org. Synth.*, **20**, 50; (*b*) *J. Amer. Chem. Soc.*, 1933, **55**, 345.

XUM

268. *The Kinetics of the Hydrolysis of Methylene Dichloride.*

By I. Fells and E. A. Moelwyn-Hughes.

The kinetics of the hydrolysis of methylene dichloride have been investigated at various temperatures in acidic and alkaline aqueous solutions. The changes concerned resolve themselves into (1) a pseudo-unimolecular reaction between methylene dichloride and the solvent, (2) a bimolecular substitution reaction between methylene dichloride and the hydroxyl ion, and (3) an apparent third-order Cannizzaro reaction between formaldehyde and the hydroxide ion. The constants obtained for reactions (1) and (2) have been compared with the corresponding constants for methyl chloride. Those obtained for reaction (3) agree with the results obtained under different conditions by Pajunen.

The effect on the rate of hydrolysis of the C–Cl group produced by successive substitution of chlorine for hydrogen atoms in methyl chloride is unpredictable from current theories of reaction kinetics. Data for methyl chloride over a range of temperature are given by Moelwyn-Hughes,[1] and work at one temperature on the alkaline hydrolysis of chloroform has been carried out by Hine [2] and his co-workers. A semi-quantitative investigation by Petrenko-Kritshenko and Opotsky [3] in 1926 showed that methylene dichloride appeared more resistant to hydrolytic attack than other members of the chlorinated methane series, but accurate data are not available. This work gives an account of an experimental investigation of the behaviour of methylene dichloride when hydrolysed in water under acidic and basic conditions in the temperature range 353—423° K.

The Hydrolysis of Methylene Dichloride in Water.

Experimental.—A solution of pure methylene dichloride (less than 0·01% of other chlorinated methanes were present according to our analysis by vapour-phase chromatography) in conductivity water was prepared, the water having previously been freed from dissolved gases as well as electrolytes. The concentration of methylene dichloride was considerably less than the saturated value at the temperature and pressure of the kinetic run. A sample was first taken for complete hydrolysis. A series of carefully annealed Pyrex ampoules were then filled and sealed off immediately, and a final sample taken for complete hydrolysis as a check on any possible loss of vapour during filling operations. The Pyrex ampoules were placed in concentric brass safety cylinders and kept at the temperature of the run in an oil thermostat. The ampoules were removed at intervals from the thermostat and immediately chilled in iced water, and their contents analysed for products.

Thermostat. This was a well-lagged, five-gallon, cylindrical metal tank filled with Shell Tellus 74 Oil. The tank was heated by two electrical heaters, one being switched in and out by an ethylene glycol–mercury filled spiral thermoregulator activating (through a spark-eliminating device) a Sunvic relay. The temperature control was accurate to $\pm 0{\cdot}05°$ over a period of 10 days.

Purity of reagents. (*a*) Methylene dichloride (Harrington Bros. Ltd.) was purified by shaking it with concentrated sulphuric acid, aqueous sodium hydrogen carbonate, and distilled water, dried (P_2O_5) for 72 hr., and twice distilled in a three-foot fractionating column packed with glass helices. The fraction of b.p. 39·85—39·95° (corr.) was collected (lit.,[4] b. p. 39·89°).

(*b*) Distilled water which had been passed through an Amberlite resin ion-exchange column was used for making up all solutions for kinetic runs.

Analysis. Each sample was analysed for chloride ion, hydrogen ion, and formaldehyde.

(*a*) Hydrogen ion. Hydrogen ion was estimated by using standard sodium hydroxide with bromothymol-blue as indicator, nitrogen being bubbled through the solution for 10 min. before the final adjustment to remove all traces of carbon dioxide.

[1] Moelwyn-Hughes, *Proc. Roy. Soc.*, 1949, *A*, **196**, 540; 1953, *A*, **220**, 386.
[2] Hine *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 2438; 1954, **76**, 827, 2688.
[3] Petrenko-Kritshenko and Opotsky, *Ber.*, 1926, **59**, 2131.
[4] Missen, Thesis, Cambridge.

(*b*) Chloride ion. Chloride ion was estimated by a modification of Mohr's method. Solutions were neutralised with calcium carbonate, titrated to the red-brown silver chromate end-point, and then back-titrated to a lime-green colour by standard potassium chloride solution. Each end-point was repeated five times.

(*c*) Formaldehyde. The conventional sodium sulphite method of estimating formaldehyde is not suitable for the very dilute solutions (about 4 mmoles per l.) involved in this reaction, so a colorimetric method was adopted. Formaldehyde develops a violet colour when heated with chromotropic acid in the presence of concentrated sulphuric acid. A standard technique [5] was employed. Calibration curves based on standard formaldehyde solutions were prepared, and the optical density of the " unknown " solution compared with them. A Unicam quartz spectrophotometer operating with light of 570 mμ wavelength was used to measure optical density.

A polarographic method, due to Boyd and Bambach,[6] was also used to determine the concentration of formaldehyde. A Cambridge Instrument Company recording polarograph with a thermostat added was used to obtain the polarograms of carefully standardised samples. A carrier of potassium hydroxide and potassium chloride was used, the polarograms were recorded photographically, and the concentration of formaldehyde deduced by comparing wave heights with those obtained by using standard samples. By this method the concentrations of formaldehyde (in moles/l.) was found to be one half of that of hydrochloric acid up to the half-life of the reaction. When the reaction had proceeded further this method proved unreliable without a more accurate stabilisation of pH, but by the colorimetric method this ratio was obtained at all stages of the reaction.

The net chemical change taking place during the acid hydrolysis of methylene dichloride is its quantitative conversion into formaldehyde:

$$CH_2Cl_2 + H_2O \xrightarrow{k_1} CH_2O + 2HCl$$

Kinetic Analysis.—The hydrolysis of methylene dichloride in acidic solution follows a simple, first-order law. The hydrogen ion, chloride ion, and formaldehyde concentrations keep abreast with one another precisely. The only deviation is a slight falling off in the velocity constant after the three-quarter life period.

The first-order constant k_1 is calculated from the slopes of plots of the logarithm of the concentration of methylene dichloride against time by using the equation $k_1 = (1/t) \ln a/(a - x)$, where a is the initial concentration of methylene dichloride and $a - x$ its concentration at time t. The results of a specimen run are given in Table 1. Since the concentrations of hydrogen ion, chloride ion, and formaldehyde agree with one another precisely within the limits of accuracy of the methods employed, the chloride-ion values are chiefly used in calculating k_1 as they are the most accurate.

TABLE 1. *Acid hydrolysis of methylene dichloride at* 373·16° K.

$10^7 \times k_1 = 5{\cdot}77 \pm 0{\cdot}05$ sec.$^{-1}$

	x (mmoles/l.)				x (mmoles/l.)		
Time (min.)	Obs. from Cl^- estn.	Obs. from H·CHO estn.	Calc. as $a[1 - \exp(k_1 t)]$	Time (min.)	Obs. from Cl^- estn.	Obs. from H·CHO estn.	Calc. as $a[1 - \exp(k_1 t)]$
0	0	0	0	22,589	14·56	14·4	14·99
3,872	3·59	3·3	3·46	28,349	16·63	16·2	17·28
8,192	6·72	7·0	7·10	70,286	24·09	—	25·18
12,509	9·62	9·6	9·72	∞	27·63	—	27·63
18,269	12·96	12·5	12·95				

Measured half-life period = 19,800 min.

The values of k_1 found at different temperatures do not conform with the integrated form of the Arrhenius equation but can be represented by the equation

$$\log_{10} k_1 = 98{\cdot}4408 - 29{\cdot}66 \log_{10} T - 10{,}597{\cdot}3/T \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Values for E_A (the Arrhenius activation energy) are 25,590 ± 350 cal. at 388° K and 24,080 ± 350 cal. at 414° K. The change of E_A with temperature is given by $dE_A/dT = -59 \pm 26$ cal./deg.

[5] Bricker and Johnson, *Ind. Eng. Chem. Anal.*, 1945, **17**, 400—402.
[6] Boyd and Bambach, *ibid.*, 1943, **15**, 314—315.

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A comparison of the observed values of k_1 and those reproduced by equation (1) is given in Table 2. The observed values of k_1 are correct to $\pm 1\%$. A four-fold change in the initial

TABLE 2.

T (°K)	373·16	392·96	403·31	415·20	424·41
$10^7 k_1$ (sec.$^{-1}$), calc.	5·75	33·4	77·4	184	339
$10^7 k_1$ (sec.$^{-1}$), obs.	5·76	30·3	77·3	187	339

concentration of methylene dichloride does not change the value of k_1 by more than 2%: at 373·16° K, $k_1 = 5{\cdot}77$ sec.$^{-1}$ for $a = 27{\cdot}63$ mmole/l. and $k_1 = 5{\cdot}93$ sec.$^{-1}$ for $a = 105{\cdot}25$ mmole/l. Thus the change of k_1 with change in initial concentration of methylene dichloride is small.

Discussion.—The net reaction is quantitatively established as being that given on p. 1327. It is possible, or even probable, that the reaction takes place in two stages of which the first is

$$CH_2Cl_2 + HOH \longrightarrow CH_2Cl{\cdot}OH + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad (I)$$

followed by one of the two conceivable subsequent reactions

$$CH_2Cl{\cdot}OH \longrightarrow CH_2O + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (IIa)$$

or

$$CH_2Cl{\cdot}OH + HOH \longrightarrow CH_2(OH)_2 + HCl \longrightarrow CH_2O + H_2O + HCl \quad . \quad (IIb)$$

In these equations formaldehyde in aqueous solution has been given the formula CH_2O although some, or most of it, is probably [6a] present as methylene glycol $CH_2(OH)_2$. Reaction (II*a*) is more likely to occur than (II*b*). The second reaction must be rapid compared with the first, which consequently determines the net rate. If the reaction intermediate postulated were present in analytically detectable amounts its effect would be detected in the kinetic measurements, and in the earlier stages of the reaction more hydrochloric acid would be formed than formaldehyde. Experimentally it is found that hydrochloric acid and formaldehyde are produced in equivalent concentrations from the beginning of the reaction. The polarographic analysis is the significant result here, as the colorimetric analysis involves treatment of the sample with concentrated sulphuric acid at 100°, which would certainly convert any unstable intermediate into formaldehyde. The simple first-order nature of the kinetic runs proves that the reaction intermediate postulated is always present in subanalytical concentrations.

The only deviation from straightforward first-order behaviour shown by the experimental results is a slight falling off in reaction rate after the three-quarter life period. Litterscheid and Thimme [7] have studied the action of excess of hydrogen chloride on formaldehyde in the presence of cold concentrated sulphuric acid, finding that dichlorodimethyl ether is formed in 85% yield. The reaction mechanism suggested by them involves the same reaction intermediate as is postulated in the hydrolysis mechanism. When the reaction mixture is warmed, however, some methylene dichloride is formed, according to Schneider.[8]

In order to test this idea of a reversibility of reaction, equilibrium constants have been calculated, first for the system

$$CH_2Cl_2 + H_2O \rightleftharpoons CH_2O + 2HCl$$

in the ideal vapour phase at 25° C and secondly in aqueous solution at the same temperature by allowing for the free-energy changes attending the dissolution of each component.

Thermodynamic Calculations.—(a) *Equilibrium in the vapour phase.* From the heats of formation, which are −21,700 cal. (CH_2Cl_2), −57,800 cal. (H_2O), −28,700 cal. (H·CHO),

[6a] See Walker, "Formaldehyde," Rheinhold, New York, 1953.
[7] Litterscheid and Thimme, *Annalen*, 1904, **334**, 1.
[8] Schneider, *Angew. Chem.*, 1938, **51**, 274.

and −22,060 cal. (HCl), the gain in heat content obtained in the vapour-phase hydrolysis is $\Delta H^\circ = 6680$ cal. The molar entropies in the standard states are 64·65 (CH_2Cl_2), 45·106 (H_2O), 52·23 (H·CHO), and 44·62 cal. (HCl). ΔS° is therefore 31·71 cal. Thus $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ = -2775$ cal. Then, substituting in $\Delta G^\circ = -RT \ln K_p$, we find that $K_p = 108$. In the equilibrium

$$\underset{(a-x)}{CH_2Cl_2} + \underset{(a-x)}{H_2O} \rightleftharpoons \underset{x}{CH_2O} + \underset{2x}{2HCl}$$

the concentrations given are equilibrium concentrations, so that $2x^2/(a-x)^2 = 108$, and, therefore $x/a = 0{\cdot}87$. This is approximately the yield reported by Michael [9] for the vapour-phase hydrolysis of methylene dichloride by steam over a catalyst at 285° c. He reports yields of 85—90%. Raising the temperature does not seem seriously to affect the equilibrium position.

(b) *Equilibrium in aqueous solution.* For the equilibrium in solution the free-energy change on dissolving each component in water must be added to the free-energy terms already calculated in the gas phase; *i.e.*,

$$\Delta G^\circ(\text{aq}) = \Delta G^\circ(\text{g}) + \sum \Delta G^\circ(\text{diss.})$$

$$\sum \Delta G^\circ(\text{diss.}) = 2\Delta G^\circ(\text{diss.})\ HCl + \Delta G^\circ(\text{diss.})\ H{\cdot}CHO \Delta G^\circ(\text{diss.})\ CH_2Cl_2 - \Delta G^\circ(\text{diss.})\ H_2O$$

Now $\Delta G^\circ(\text{aq}) = \Delta G^\circ(\text{g}) + \sum RT \ln r_i$, where r = Henry's constant, except in the case of water, for which $\Delta G^\circ(\text{diss.}) = RT \ln (p^\circ/760)$, where p° = vapour pressure of water (in mm. Hg) at temperature T. Hence, we have

	ΔG°(diss.) (cal./mole)		ΔG°(diss.) (cal./mole)
CH_2Cl_2	570	CH_2O	−5000
H_2O	−2194	HCl	−8890

$\sum \Delta G^\circ(\text{diss.}) = -21{,}156$; ΔG° (aq.) $= -2{,}775 - 21{,}156 = -23{,}931$ cal.; $K = 3{\cdot}63 \times 10^{17}$.

Data for these calculations have been obtained from a variety of sources. Heats of formation are from Bichowski and Rossini.[10] Absolute entropies for water and hydrogen chloride were obtained from the National Bureau of Standards [11] publications. The values for formaldehyde and methylene dichloride have been calculated by evaluating the molecular partition function (f), using Herzberg's data,[12] and substituting in the relation $S = N_o k[\ln f + T(\mathrm{d} \ln f/\mathrm{d}T)_v]$.

The free-energy change on dissolution for formaldehyde was obtained from Parkes and Huffman,[13] for hydrogen chloride from Ellis's vapour-pressure data,[14] for water by using tabulated vapour pressures given by Kaye and Laby,[15] and for methylene dichloride the solubility–vapour pressure data were obtained experimentally.

The reaction clearly goes effectively to completion in aqueous solution, and the falling off in the velocity constant cannot therefore be accounted for by supposing the products are recombining to form the reactants.

Another suggestion is the effect of increasing ionic strength on the reaction intermediate as the reaction proceeds, since the rearrangement of charge distribution in the transition complex may be considerably affected by the increased concentration of ions in its vicinity.

[9] Michael, G.P. 382,391; *Chem. Zentr.*, 1924, I, 1710.
[10] Bichowski and Rossini, "Thermochemistry of Chemical Substances," Rheinhold, New York, 1936.
[11] National Bureau of Standards, Series III, Vol. 1.
[12] Herzberg, "Infra-Red and Raman Spectra," D. Van Nostrand Co. Inc., New York, 1945.
[13] Parkes and Huffman, "Free Energies of Some Organic Compounds," Reinhold, New York, 1932.
[14] Ellis, *J. Amer. Chem. Soc.*, 1916, **38**, 737.
[15] Kaye and Laby, "Physical and Chemical Constants," Longmans, Green, London, 1948.

XUM

Hydrolysis of Methylene Dichloride in Aqueous Potassium Hydroxide

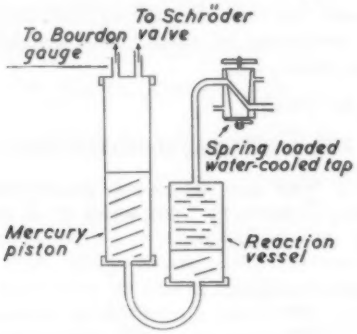
The kinetics of the hydrolysis of methylene dichloride in alkaline solution has been examined by using potassium hydroxide as hydrolysing agent. The concurrent reactions

$$CH_2Cl_2 + HOH \xrightarrow{k_1} CH_2O + 2HCl \text{ and } CH_2Cl_2 + 2OH^- \xrightarrow{k_2} CH_2O + 2Cl^-$$

have been investigated over the temperature range 350—404° K.

Experimental.—The reactions were carried out in the absence of the vapour phase in a nickel reaction vessel of 300 ml. capacity, closed by a mercury piston which could be pumped to 4 atm. pressure. Samples were removed through a heavy, steel, water-cooled, spring-loaded tap. The reaction vessel was completely immersed in the oil thermostat previously described. A diagram of the apparatus is shown in Fig. 1.

FIG. 1.



Analysis. (a) Hydroxide ion. This was estimated by using standard nitric acid with bromothymol-blue as indicator, nitrogen being bubbled through the solution for 10 min. as before.

(b) Chloride ion. This was estimated as before.

(c) Formaldehyde. This was estimated polarographically. Since the reaction proceeds in a solution of potassium hydroxide and potassium chloride, comparisons with polarograms of standard solutions of formaldehyde are easily made, as the carrying solution consists of potassium hydroxide and potassium chloride. The wave height varies with KOH : KCl ratio; standard solutions having carrying solutions of different KOH : KCl ratios were therefore prepared, and the requisite standard for comparison selected. Unchanged methylene dichloride does not intefere in the estimation as the half wave for formaldehyde occurs at −1·63 v (S.C.E.) and for methylene dichloride at −2·33 v.

Kinetic Analysis and Results.—Reaction between between methylene dichloride and potassium hydroxide in aqueous solution is not a simple second-order reaction. Reaction with the solvent occurs, and in addition the formaldehyde formed reacts with the potassium hydroxide, giving methyl alcohol and formic acid (Cannizzaro's reaction, 3 below). The methyl alcohol can in turn react with the formaldehyde to give methylal. Under the alkaline conditions prevailing it is also possible for the formaldehyde formed to polymerise to sugars:

$$(1)\quad CH_2Cl_2 + HOH \xrightarrow{k_1} CH_2O + 2H^+ + 2Cl^-$$

$$(2)\quad CH_2Cl_2 + 2OH^- \xrightarrow{k_2} CH_2O + 2Cl^- + H_2O$$

$$(3)\quad 2CH_2O + OH^- \longrightarrow H{\cdot}CO_2^- + CH_2{\cdot}OH$$

$$(4)\quad 2CH_2{\cdot}OH + CH_2O \longrightarrow CH_2(OCH_3)_2 + H_2O$$

$$(5)\quad nCH_2O \longrightarrow (CH_2O)_n$$

Under the conditions of our experiments, reactions (4) and (5) do not occur.

The bimolecular velocity constants for the reaction between methylene dichloride and hydroxide ion have been found by using the equation

$$-\mathrm{d}[CH_2Cl_2]_t/\mathrm{d}t = k_1[CH_2Cl_2]_t + k_2[CH_2Cl_2]_t[OH^-]_t$$

The values of $-\mathrm{d}[CH_2Cl_2]_t/\mathrm{d}t$ are obtained by drawing tangents to the progress curve at equally spaced intervals from zero time to the three-quarter life period. The values accepted as the most reliable are those obtained when the reaction is between 25% and 70% complete. When it is less than 10% complete bimolecular constants can be obtained by using the integrated equation

$$t = \frac{1}{k_1 + k_2(b - 2a)}\left\{\ln \frac{a}{(a - x)} \frac{[k_1 + k_2(b - 2x)]}{(k_1 + k_2 b)}\right\}$$

where $a = [CH_2Cl_2]_0$, $b = [OH^-]_0$, and $(a - x) = [CH_2Cl_2]_t$. This equation ignores the Cannizzaro reaction, which does not proceed to any appreciable extent at the beginning of the reaction.

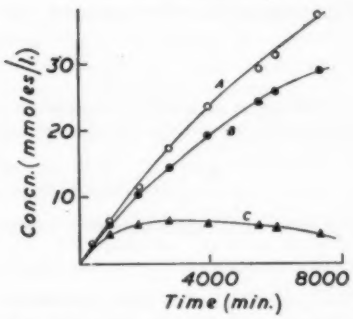


FIG. 2. *A, rate of removal of* OH^-; *B, rate of formation of* Cl^-; *C, rate of formation of* H·CHO.

$[CH_2Cl_2]_0 = 25{\cdot}15$ mmoles/l., $[KOH]_0 = 109{\cdot}0$ mmoles/l., $T = 352{\cdot}96°$ K, $10^5k_2 = 2{\cdot}071$./mole^{-1} sec.$^{-1}$, $k_3 = 0{\cdot}0146$ l.^{2} mole^{-2} sec.$^{-1}$.

A set of data from a typical kinetic run is shown in Fig. 2; the rise and fall of the formaldehyde concentration and the divergence of the hydroxide-ion and chloride-ion progress curves are clearly shown. The values for k_2 are obtained by drawing tangents to the progress curve; k_1 values are obtained from equation (1).

Analysis of all the results obtained in this way shows that the reaction between methylene dichloride and hydroxide ion is definitely of the second order although stoicheiometrically one molecule of methylene dichloride reacts with two molecules of hydroxide ion.

TABLE 3.

T (°K)	352·96	376·18	385·42	395·22	404·26
10^5k_2 (l. moles^{-1} sec.$^{-1}$), calc.	2·03	21·7	50·3	117	249
10^5k_2 (l. moles^{-1} sec.$^{-1}$), obs.	2·09	22·0	48·6	114	244

The values obtained for k_2 conform to the Arrhenius equation $\log_{10} k_2 = 11{\cdot}5669 - 5730{\cdot}2/T$, with $E_A = 26{,}221 \pm 450$ cal. Table 3 shows the calculated and observed values of k_2. The observed values of k_2 have been corrected for the expansion of the solvent and resultant concentration change over the temperature range used, and are correct to $\pm 4\%$. An increase in hydroxide-ion concentration of 100% raises the value of k_2 by less than 1%. The concentration of hydroxide ion used is just sufficient to react with all the methylene dichloride present.

- The Cannizzaro Reaction between Formaldehyde and Potassium Hydroxide as a Consecutive Reaction in the Alkaline Hydrolysis of Methylene Dichloride.—The reaction between formaldehyde and hydroxide ion has been investigated by a variety of workers. Pajunen [16] gives third-order constants which, over a range of temperature, conform to the Arrhenius equation. More recent papers by Abel [17] and Martin [18] show that the reaction is not of third order but consists of two reactions, one of the third and one of the fourth order, proceeding simultaneously. Consistent

[16] Pajunen, *Suomen Kem.*, 1948, **21**, *B*, 21—24; *Ann. Acad. Sci. Fenn.*, Ser. *A*, II, Chemica, 1950, **37**, 7—60.
[17] Abel, *Z. phys. Chem.* (*Frankfurt*), 1954, **1**, 201.
[18] Martin, *Australian J. Chem.*, 1954, **7**, 335—347.

third-order constants can be obtained during any one run, but variation of the initial formaldehyde and hydroxide-ion concentrations results in a variation of the constant. All previous work has been carried out in the temperature range 40—60° with relatively concentrated solutions (0·1M-formaldehyde and 0·05M-potassium hydroxide). Above 70°, aldol condensation to sugars is said to take place. Loew [19] has obtained hexose sugars in 75% yield, and Katzschmann [20] has suggested an autocatalytic mechanism for sugar formation involving bishydroxymethylacetol as catalyst. This he isolated and identified.

In this work the concentration of potassium hydroxide is approximately the same as that used by Pajunen.[16] The formaldehyde concentration, however, never rises above 5 mmoles/l. and is generally less. The reaction has been followed from 80° to 120°; in this range and under the conditions specified, the formaldehyde is removed almost as quickly as it is formed. Third-order constants in good agreement with values obtained by extrapolating Pajunen's values [16] have been obtained.

The third-order constants have been obtained in two ways. In those reactions in which a maximum appears in the formaldehyde progress curve the rates of its appearance and disappearance have been equated. Thus

$$k_3 = \frac{k_1[CH_2Cl_2]_t + k_2[CH_2Cl_2]_t[OH^-]_t}{[H{\cdot}CHO]_t^2[OH^-]_t}$$

For reactions in which no maximum appears, tangents have been drawn to the hydroxide-ion progress curve and the k_3 values obtained from the following differential equation

$$k_3 = \frac{1}{[H{\cdot}CHO]_t^2[OH^-]_t}\left\{-\frac{d[OH^-]_t}{dt} - 2[CH_2Cl_2]_t(k_2[OH^-]_t + k_1)\right\}$$

The series of k_3 values obtained conform to the Arrhenius equation

$$\log_{10} k_3 = 11{\cdot}7669 - 4{,}819{\cdot}8/T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (III)$$

This is in remarkably close agreement with the equation given by Pajunen based on work done in the temperature range 40—70°, *viz.*,

$$\log_{10} k_3 = 11{\cdot}9042 - 4{,}877{\cdot}5/T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (IV)$$

Table 4 shows the observed and calculated values of k_3 obtained in this work and those obtained by Pajunen; k_3 values from equations (III) and (IV) are quoted over the total temperature range. The accuracy of the experimental values of k_3 obtained by the two methods described is $\pm 10\%$. As the concentration of formaldehyde is never greater than 5 mmoles/l. the accuracy of the rate constants is limited by the accuracy with which dilute formaldehyde solutions can be analysed.

TABLE 4.

	k_3 (l.^{2} mole^{-2} sec.$^{-1}$)					k_3 (l.^{2} mole^{-2} sec.$^{-1}$)			
Temp.	This work		Pajunen's work		Temp.	This work		Pajunen's work	
(°K)	Obs.	Calc.	Calc.	Obs.	(°K)	Obs.	Calc.	Calc.	Obs.
313·16	—	0·000243	0·000209	0·000212	353·04	0·0136	0·0133	0·0123	—
323·16	—	0·000727	0·000636	0·000624	363·55	0·0316	0·0329	0·0308	—
333·16	—	0·00203	0·00180	0·00175	376·16	0·087	0·0916	0·0867	—
343·16	—	0·00537	0·00422	0·00491	385·42	0·206	0·186	0·178	—
					395·22	0·366	0·379	0·366	—

[H·CHO] varies from 0 to 5 mmoles/l.; [KOH] varies from 30 to 80 mmoles/l.

Both Abel [17] and Martin [18] have suggested mechanisms for the Cannizzaro reaction involving ionisation of a formaldehyde molecule to $CH_2(OH){\cdot}O^-$ and $CH_2O_2^{2-}$ ions. A rigorous examination of a series of runs at one temperature with different formaldehyde and hydroxyl-ion concentrations shows both third- and fourth-order kinetics. Martin has suggested that third-order constants together with reactant concentrations be quoted, and this suggestion has been followed here. Rate constants based on a simple third-order mechanism are pH dependent. The hydroxide-ion concentrations used in this work are the same as those used by Pajunen [16] and it is for this reason that a comparison of the results is possible.

These results show that under conditions of constant pH and in a system in which the

[19] Loew, *Ber.*, 1887, **20**, 144.
[20] Katzschmann, *Ber.*, 1944, **77**, 579—585.

formaldehyde concentration is low during the entire course of the run the Cannizzaro reaction occurs up to 120°, with negligible condensation of the formaldehyde to sugars. At 130° the kinetic runs indicate that some sugar formation occurs although the Cannizzaro reaction still proceeds.

Discussion

The hydrolysis of methylene dichloride in neutral or acidic aqueous solution closely resembles that of methyl chloride but is about 200 times slower. Kinetically, the reaction is of the pseudo-first order, the rate at any instant being proportional to the concentration of solute. The rate-determining step may be simply

$$CH_2Cl_2 + nH_2O \longrightarrow CH_2O + 2[H,mH_2O]^+ + 2[Cl,\{\tfrac{1}{2}(n-1) - m\}H_2O]^-$$

where m and n are solvation numbers, or it may be

$$CH_2Cl_2 + nH_2O \longrightarrow CH_2Cl(OH) + [H,mH_2O]^+ + [Cl,(n-1-m)H_2O]^-$$

followed by a relatively rapid second reaction. The apparent energies of activation for the hydrolyses of methyl chloride and methylene dichloride are equal, within the accuracy of the work, being, *e.g.*, 25,200 and 25,600 cal. at the b. p. of the solvent. The temperature variations of the apparent energies of activation are also approximately the same.

In alkaline solution, the pseudo-first-order reaction with the solvent takes place simultaneously with several other reactions, of which the first to be considered is the bimolecular substitution reaction $CH_2Cl_2 + 2OH^- \longrightarrow CH_2O + 2Cl^-$, which is found to be of the first kinetic order with respect to each reactant and therefore to be a reaction of the second order. As in the hydrolytic change, the second substitution must be relatively rapid and may, in fact, be an elimination rather than a substitution. As is usual with bimolecular reactions between ions and polar molecules, no variation of the apparent energy of activation of this reaction with respect to temperature could be detected. The bimolecular velocity constant at 373·16° K is lower than that for the reaction between methyl chloride and the hydroxide ion by a factor of 154, and the energy of activation is higher by 1940 cal. Thus the relative slowness is due only in part to an increase in the activation energy. It is noteworthy that the effect of substituting a chlorine atom for one of the hydrogen atoms in methyl chloride should reduce the rate more effectively than does the substitution of a charged carboxyl group, as shown here:

Reaction	k_2 at 373·16° K (l. mole^{-1} sec.$^{-1}$)	A (l. mole^{-1} sec.$^{-1}$)	E_A (cal./mole)
$CH_3Cl + OH^-$	$2{\cdot}48 \times 10^{-3}$	$4{\cdot}11 \times 10^{12}$	24,280
$CH_2Cl_2 + OH^-$	$1{\cdot}61 \times 10^{-4}$	$3{\cdot}69 \times 10^{11}$	26,220
$CH_2Cl{\cdot}CO{\cdot}O^- + OH^-$	$3{\cdot}22 \times 10^{-4}$	$4{\cdot}55 \times 10^{11}$	25,850

Finally, the instantaneous rate of production of formate ions and methanol according to the Cannizzaro reaction

$$2CH_2O + OH^- \longrightarrow H{\cdot}CO{\cdot}O^- + CH_3{\cdot}OH$$

is found to be proportional to the concentration of hydroxyl ion and to the square of the concentration of formaldehyde under the conditions of the experiments. The reaction is therefore effectively a reaction of the third kinetic order. The magnitude of the pre-exponential term in the Arrhenius equation, however, is somewhat greater than that expected from the frequency of ternary collisions, but is not inconsistant with the mechanism suggested by Abel,[17] according to which the rate-determining step is that between molecules of formaldehyde and the charged complexes $[HO{\cdot}CH_2{\cdot}O]^-$ and $[CH_2O_2]^{--}$, the equilibrium concentrations of which are proportional to $[H{\cdot}CHO][OH^-]$ and $[H{\cdot}CHO][OH^-]^2$, respectively.

The authors thank British Celanese Ltd. for a grant to one of them (I. F.) which made this work possible.

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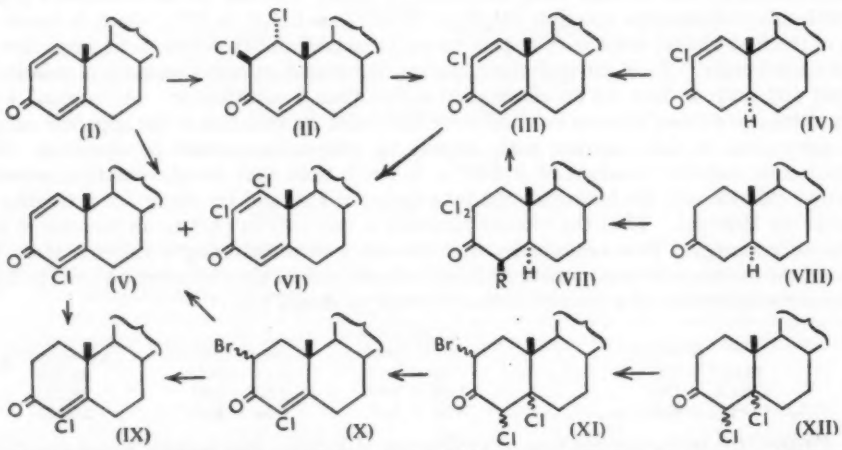
[*Received, October 25th*, 1957.]

269. *Modified Steroid Hormones. Part IX.* The 2- and 4-Chloro-derivatives of 17β-Propionoxyandrosta-1 : 4-dien-3-one and -1 : 4 : 6-trien-3-one.*

By David N. Kirk and Vladimir Petrow.

Methods have been developed for the conversion of cholesta-1 : 4-dien-3-one (I) and -1 : 4 : 6-trien-3-one (XVII) into their 2- and 4-chloro-derivatives and have been applied to the preparation of the compounds named in the title, which were required for biological study.

The conversion of 3-oxo-Δ^4-steroids into 4-bromo- and 4-chloro-3-oxo-Δ^4-steroids was described in Parts I [1] and III.[2] 4-Bromo-3-oxo-Δ^4-steroids were prepared by bromination in the presence of proton-acceptors such as pyridine, ethylene oxide, or propylene oxide. The 4-chloro-derivatives were similarly obtained, by employing the same proton acceptors or dimethylformamide, and also by chlorination in ether–propionic acid to give the 4ξ : 5ξ-dichlorides, which passed readily into the 4-chloro-3-oxo-Δ^4-steroids on treatment with basic reagents such as pyridine or chromatographic alumina. An extension of these studies to the chlorination of some 1 : 4-dien-3-ones and 1 : 4 : 6-trien-3-ones is now reported.



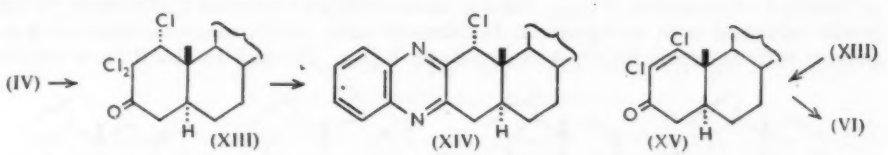
Treating the model compound cholesta-1 : 4-dien-3-one (cf. I) with 1 mol. of chlorine in ether–propionic acid caused addition of chlorine, with formation of a compound, $C_{27}H_{42}OCl_2$. That this addition involves the 1 : 2-unsaturated linkage follows from the transformations described below which lead to its formulation as 1α : 2β-dichlorocholest-4-en-3-one (II), it being assumed that this addition gives a *trans*-diaxial dichloride.[3] The axial β-orientation of the 2-chlorine atom is supported by the ultraviolet absorption maximum at 250—251 mμ, in contrast to the value of 246 mμ shown by 2α-chlorocholest-4-en-3-one:[4,5] the bathochromic shift at 4—5 mμ which occurs in passing from the equatorial α- to the axial β-configuration of the 2-halogen atom accords well with the difference of 5 mμ observed by Ellis and Petrow [5] between 2α- ($\lambda_{max.}$ 249 mμ) and 6β-bromo-2β-chlorocholest-4-en-3-one ($\lambda_{max.}$ 254 mμ).

* Part VIII, *J.*, 1958, 800.

[1] Kirk, Patel, and Petrow, *J.*, 1956, 627.
[2] *Idem*, *J.*, 1956, 1184.
[3] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370, and earlier refs. therein.
[4] (*a*) Ellis and Petrow, *J.*, 1953, 3869; (*b*) Beereboom and Djerassi, *J. Org. Chem.*, 1954, **19**, 1196.
[5] Ellis and Petrow, *J.*, 1956, 1179.

Reaction of the dichloride (II) with pyridine at room temperature led to a monochloro-derivative, $C_{27}H_{41}OCl$, considered to be 2-chlorocholesta-1 : 4-dien-3-one (III) on the basis of (i) its infrared absorption band at 6·02 μ (dienone [6]), (ii) its stability to boiling collidine and to lithium chloride in dimethylformamide, and (iii) its conversion into a 2 : 4-dinitrophenylhydrazone without loss of halogen, the last two observations being incompatible with a 6-chloro-structure.[7] This formulation (III) was finally established by comparison with authentic 2-chlorocholesta-1 : 4-dien-3-one obtained by dehydrogenation of 2-chlorocholest-1-en-3-one (IV) with selenium dioxide.[8] The same chloro-dienone (III) was also formed when either 4β-bromo-2 : 2-dichlorocholestanone (VII; R = Br), obtained by bromination of 2 : 2-dichloro- (VII; R = H) [4a] or 2 : 2 : 4β-trichloro-cholestanone (VII; R = Cl), prepared by trichlorination of cholestanone (VIII), was treated with boiling collidine. The β-configuration is assigned to the 4-halogeno-substituent in the trichloro-ketone (VII; R = Cl) by analogy with the preferred formulation of the bromo-analogue [9] (VII; R = Br).

Reaction of cholesta-1 : 4-dien-3-one (I) with 1 mol. of chlorine in dimethylformamide gave, in place of dichlorocholestenone (II), a mixture which was separated by chromatography on alumina into (i) a new monochlorocholestadienone, (ii) a dichlorocholestadienone, and (iii) unchanged material. Increasing the proportion of chlorine used led only to the disappearance of unchanged material from the product, which still consisted of the same mono- and dichloro-derivatives in approximately equal amounts: the significance of this observation is referred to below.



Formulation of the new monochloride as 4-chlorocholesta-1 : 4-dien-3-one (V) was indicated by its infrared absorption band at 6·02 μ (1 : 4-diene-3-one [6]), and its stability in boiling collidine. Evidence supporting its formulation as a 4-chloro-derivative was also obtained by its alternative preparation from 4ξ : 5ξ-dichlorocholestan-3-one [2] (XII). The last-mentioned compound in acetic acid gave 2ξ-bromo-4ξ : 5ξ-dichlorocholestan-3-one (XI), which with pyridine at room temperature afforded 2ξ-bromo-4-chlorocholest-4-en-3-one (X), readily transformed into the foregoing monochlorodienone (V) by dehydrobromination with collidine or lithium chloride–dimethylformamide. The constitution of the key intermediate (X) follows from its ultraviolet absorption spectrum ($\lambda_{max.}$ 260 mμ) and from its conversion into 4-chlorocholest-4-en-3-one (IX) by reduction with zinc dust in acetic acid. The new monochloride (V) is proved finally to be a 4-chloro-derivative by catalytic hydrogenation to 4-chlorocholest-4-en-3-one (IX). *Inter alia* we attempted to prepare the chloro-ketone (V) by dehydrogenating 4-chlorocholest-4-en-3-one with selenium dioxide, but obtained a gum.

The presence of a 1 : 4-dien-3-one system in the foregoing dichlorocholestadienone was revealed by its ultraviolet (max. at 258 mμ) and infrared (band at 6·02 μ) absorption spectra. That the chlorine atoms were situated in two of the vinylic positions 1, 2, and 4 was apparent from the stability of the compound to collidine and to lithium chloride–dimethylformamide. Recognition of a 2-chloro-ketone followed from its formation from the 2-chloro-dienone (III) by monochlorination. Its formulation as 1 : 2-dichlorocholesta-1 : 4-dien-3-one (VI) was established as follows.

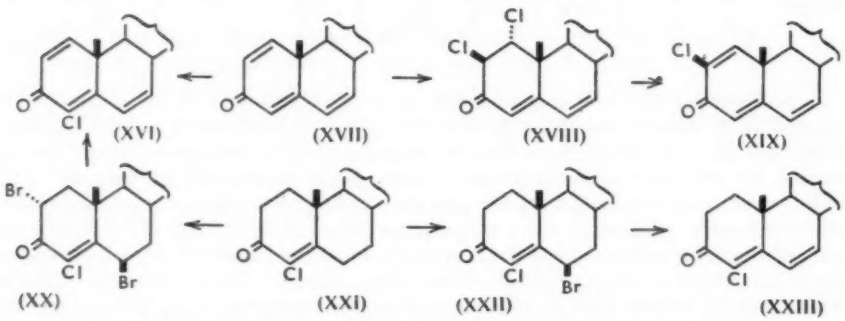
Monochlorination of cholest-1-en-3-one gave the expected 2-chlorocholest-1-en-3-one

[6] Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.
[7] Ginsburg, *J. Amer. Chem. Soc.*, 1953, **75**, 5489.
[8] Meystre, Frey, Voser, and Wettstein, *Helv. Chim. Acta*, 1956, **39**, 734.
[9] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.

(IV), there being evidence for initial formation of an unstable 1 : 2-dichloride. Further chlorination led to the stable 1α : 2 : 2-trichlorocholestan-3-one (XIII) (cf. ref. **3** for configuration at $C_{(1)}$), characterised by absorption in the *R*-band region ($\lambda_{max.}$ 296 mμ) nearly identical with that reported [10] for 2 : 2-dichlorocholestan-3-one [1] ($\lambda_{max.}$ 294 mμ) and by reaction with *o*-phenylenediamine to give the chloroquinoxaline (XIV). Dehydrochlorination of the trichloro-compound (XIII) with lithium chloride–dimethylformamide led to 1 : 2-dichlorocholest-1-en-3-one (XV), whose dinitrophenylhydrazone was formed without loss of halogen, confirming the absence of a 4-halogen atom. This ketone (XV) was smoothly dehydrogenated by selenium dioxide [8] to 1 : 2-dichlorocholesta-1 : 4-dien-3-one (VI), identical with the material obtained as above.

Substitution of chlorine at position 2 or 4 in cholestadienone (I) decreases the reactivity of the ketonic function presumably by virtue of the $-I$ effect of the halogen on the polarisation of the carbonyl group. Thus the monochloro-ketones (III) and (V) fail to react with *o*-phenylenediamine (cf. Parts I [1] and III [2]). They condense normally, though somewhat sluggishly, with 2 : 4-dinitrophenylhydrazine. The dichloro-ketone (VI), in contrast, fails to react even with the last reagent. *Inter alia*, they do not form 3 : 3-ethylenedioxy-derivatives [11] or 3-enamine derivatives.[12]

Chlorination of cholesta-1 : 4 : 6-trien-3-one (XVII) followed the pattern established for the dienone (I). In ether–propionic acid the trienone reacted additively, to give 1α : 2β-dichlorocholesta-4 : 6-dien-3-one (XVIII). The constitution assigned to this compound is supported by its ultraviolet absorption ($\lambda_{max.}$ 299 mμ) which is consistent with a cholesta-4 : 6-dien-3-one [13] ($\lambda_{max.}$ 284 mμ) substituted with an axial 2-chlorine atom but hardly consistent with an equatorial 2α-chloro-structure which would be expected from analogy with 2α-bromocholesta-4 : 6-dien-3-one [14] ($\lambda_{max.}$ 290 mμ) to absorb at a shorter



wavelength.[5] Dehydrochlorination of the dichloro-ketone (XVIII) with cold pyridine led to 2-chlorocholesta-1 : 4 : 6-trien-3-one (XIX) ($\lambda_{max.}$ 217, 268, and 307 mμ). This compound was additionally prepared by dichlorination of either 5α : 6β-dibromocholestan-3-one or 6β-bromocholest-4-en-3-one, to the corresponding 2 : 2-dichloro-derivative, and dehydrohalogenation of this with lithium chloride in dimethylformamide (cf. the similar preparation of 2-bromocholesta-1 : 4 : 6-trien-3-one [14]).

Chlorination of the trienone (XVII) in dimethylformamide gave 4-chlorocholesta-1 : 4 : 6-trien-3-one (XVI). There was no evidence for concomitant production of a dichloro-derivative under these conditions. The formulation (XVI) is supported by an alternative preparation from 4-chlorocholest-4-en-3-one (XXI). Monobromination of the last compound in acetic acid led to 6β-bromo-4-chlorocholest-4-en-3-one (XXII), converted

[10] Cookson, *J.*, 1954, 282.
[11] Fernholz and Stavely, Abs. 102nd Meeting Amer. Chem. Soc., Atlantic City, N.J., 39M (1941); Antonucci, Bernstein, Littell, Sax, and Williams, *J. Org. Chem.*, 1952, **17**, 1341.
[12] Johnson, Herr, Babcock, Fonken, Stafford, and Heyl, *J. Amer. Chem. Soc.*, 1956, **78**, 430.
[13] Wilds and Djerassi, *ibid.*, 1946, **68**, 1712.
[14] Fieser, Romero, and Fieser, *ibid.*, 1955, **77**, 3305.

by boiling collidine, or more efficiently by lithium chloride–dimethylformamide, into 4-chlorocholesta-4 : 6-dien-3-one (XXIII) ($\lambda_{max.}$ 298·5 mμ, revealing a bathochromic shift of 14·5 mμ due to the 4-chloro-substituent [13]). Further bromination of the 6-bromo-derivative (XXII) or dibromination of 4-chlorocholest-4-en-3-one (XXI) yielded 2α : 6β-dibromo-4-chlorocholest-4-en-3-one (XX) which passed smoothly into the foregoing 4-chlorocholesta-1 : 4 : 6-trien-3-one (XVI) on dehydrobromination with lithium chloride–dimethylformamide.

The α- and β-configurations assigned to the bromine atoms in the foregoing two compounds [(XX) and (XXII)] follow from analogy with the direct bromination of cholest-4-en-3-one,[15] which gives the 2α : 6β-dibromo-derivative.[5,14] They are supported by spectroscopic data. Thus introduction of a 4-chloro-substituent into 6β-bromocholest-4-en-3-one ($\lambda_{max.}$ 244 mμ) [15,16] leads to a bathochromic shift of 22 mμ which, though somewhat greater than that usually associated with such substitution (*ca.* 16 mμ) is nevertheless more in accord with expectation than would obtain on the basis of a 6α-bromo-formulation (cf. 6α-bromocholest-4-en-3-one,[16] $\lambda_{max.}$ 238 mμ). Absorption in the *R*-band region affords further support. The fine structure observed in the ultraviolet absorption of 4-chlorocholest-4-en-3-one (XXI) in the 300—400 mμ region is almost identical with that reported by Cookson *et al.* for cholest-4-en-3-one (cf. Table 1).

TABLE 1. $\lambda_{max.}$ (mμ) (and ε, in parentheses).

Cholest-4-en-3-one [a]	314 (45)	323·5 (49)	336 (47)	349 (34)	367 (14)
4-Chloro-4-en-3-one	313 (40)	324 (41)	337 (34)	350 [b] (19)	368 [b] (6·5)
6α-Bromo-4-en-3-one [a]	319 [b] (31)	329·5 (36)	340·5 (36)	352 [b] (28)	372 [b] (11·5)
6β-Bromo-4-en-3-one [a]	—	344 (64·5)	355 (62)	371 [b] (46·5)	391 [b] (20)
6β-Bromo-4-chlorocholest-4-en-3-one	336 (69)	345 [b] (65)	353 [b] (55)	371 [b] (31)	395 [b] (8)

[a] Values given by Bird *et al.*[17] [b] Inflexion.

Similar identity exists between the 6β-bromo-derivatives of these two ketones, which differ significantly in the *R*-band region from 6α-bromocholest-4-en-3-one.

The 2α-orientation of the bromine atom in the dibromo-ketone (XX) follows from the data in Table 2.

TABLE 2.

Compound	$\lambda_{max.}$ (mμ)	Bathochromic shift (mμ) due to 2-Br
6β-Bromocholest-4-en-3-one [15,16]	244	—
2α : 6β-Dibromocholest-4-en-3-one [14]	248	4
2β : 6β-Dibromocholest-4-en-3-one [5]	257	13
6β-Bromo-4-chlorocholest-4-en-3-one	266	—
2α : 6β-Dibromo-4-chlorocholest-4-en-3-one	270—271	4—5

Chlorination of 17β-propionoxyandrosta-1 : 4-dien-3-one (I) in ether–propionic acid furnished the 1α : 2β-dichloro-derivative (II) which was converted into 2-chloro-17β-propionoxyandrosta-1 : 4-dien-3-one (III) by brief treatment with pyridine. By performing the chlorination in dimethylformamide, 1 : 2-dichloro- (VI) and 4-chloro-17β-propionoxyandrosta-1 : 4-dien-3-one (V) were obtained, the last compound being also prepared from 4ξ : 5ξ-dichloro-17β-propionoxyandrostan-3-one (XII) *via* the 2ξ-bromo-derivatives (XI) and (X).

17β-Propionoxyandrosta-1 : 4 : 6-trien-3-one (XVII) in ether–propionic acid gave the 1α : 2β-dichloro-derivative (XVIII), which was converted into 2-chloro-17β-propionoxyandrosta-1 : 4 : 6-trien-3-one (XIX). 4-Chloro-17β-propionoxyandrosta-1 : 4 : 6-trien-3-one (XVI) was obtained by direct chlorination of the trienone (XVII) in dimethylformamide or by dibromination of 4-chloro-17β-propionoxyandrost-4-en-3-one (XXI), followed by dehydrobromination.

[15] Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534.
[16] Barton and Miller, *ibid.*, p. 1066.
[17] Bird, Cookson, and Dandegaonker, *J.*, 1956, 3675.

XUM

Experimental

Optical rotations refer to $CHCl_3$ solutions in a 1 dm. tube. Ultraviolet absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc. (values in parentheses are log ε), for EtOH solutions unless otherwise stated. Infrared absorption spectra (in Nujol) were kindly determined by Mr. R. F. Branch, B.Sc., Ministry of Supply. B.D.H. alumina, chromatography grade, was employed.

1α : 2β-*Dichlorocholest*-4-*en*-3-*one* (II).—Cholesta-1 : 4-dien-3-one (2 g.) in dry ether (50 ml.) at −30° was treated with chlorine in 1·10M-propionic acid (4·8 ml.), and the mixture stored at −30° in the dark for 20 hr. The ether was washed with water, dilute sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). Evaporation under reduced pressure and crystallisation of the residue from ether–methanol gave 1α : 2β-*dichlorocholest*-4-*en*-3-*one*, needles, m. p. 122—123°, $[\alpha]_D^{24}$ +25° (*c* 0·50), $\lambda_{max.}$ 250—251 mμ (4·14) (Found: C, 71·5; H, 9·3; Cl, 15·0. $C_{27}H_{42}OCl_2$ requires C, 71·5; H, 9·3; Cl, 15·6%).

2-*Chlorocholesta*-1 : 4-*dien*-3-*one* (III).—(*a*) The foregoing dichloride (400 mg.) in pyridine (2 ml.) was set aside for 4 hr., pyridine hydrochloride separating. After dilution with ether and dilute hydrochloric acid, the ether layer was washed, dried, and evaporated. The residue was purified from hexane or aqueous acetone, to give 2-*chlorocholesta*-1 : 4-*dien*-3-*one*, fibrous crystals, m. p. 128—130°, $[\alpha]_D^{23}$ +8° (*c* 0·46), $\lambda_{max.}$ 253 mμ (4·20), ν 6·02 μ (Found: C, 77·6; H, 9·8; Cl, 9·0. $C_{27}H_{41}OCl$ requires C, 77·6; H, 9·9; Cl, 9·3%).

(*b*) 2-Chlorocholest-1-en-3-one (1·72 g.) in a solution of selenium dioxide (0·6 g.) and acetic acid (0·5 ml.) in *tert.*-butyl alcohol (45 ml.) was heated under reflux under nitrogen for 12 hr., then 0·6 g. selenium dioxide was added and boiling continued for a further 20 hr. The cooled solution was diluted with ether, filtered from selenium, washed with sodium hydrogen carbonate solution and water, dried, and evaporated. The red-brown residue in benzene–light petroleum (1 : 4) was percolated through chromatographic alumina (5 g.). Evaporation of the solvent gave 2-chlorocholesta-1 : 4-dien-3-one, m. p. and mixed m. p. 127—128° with the sample prepared above.

(*c*) 4β-Bromo-2 : 2-dichlorocholestan-3-one (VII; R = Br) (1 g.) in collidine (7 ml.) was heated under reflux under nitrogen for 30 min. The cooled mixture was poured into dilute sulphuric acid, and the product isolated with ether. The product in benzene solution was percolated through alumina (5 g.), then crystallised from hexane to give 2-chlorocholesta-1 : 4-dien-3-one, m. p. and mixed m. p. 125—128°, with samples prepared as above.

(*d*) Cholestan-3-one (2 g.) in carbon tetrachloride (20 ml.) and acetic acid (10 ml.) was treated with a 1·05M-solution of chlorine in propionic acid (15 ml.; 3 mols.) at room temperature for 72 hr. whereafter no free chlorine remained. 2 : 2 : 4β-*Trichlorocholestan*-3-*one*, isolated with ether, formed needles, m. p. 116—117° (Found: C, 66·5; H, 8·7; Cl, 19·8. $C_{27}H_{43}OCl_3$ requires C, 66·2; H, 8·8; Cl, 21·7%), after crystallisation from acetone–methanol.

The trichloro-derivative (800 mg.) in collidine (10 ml.) was heated under reflux under nitrogen for 25 min., to give the 2-chlorodienone, m. p. and mixed m. p. 126—127° on admixture with samples prepared as above.

The 2-*chlorocholesta*-1 : 4-*dien*-3-*one* 2 : 4-*dinitrophenylhydrazone* separated from chloroform–ethanol in plates, m. p. 247—250° (decomp.), $\lambda_{max.}$ 395 mμ (4·53) (Found: N, 10·2; Cl, 6·3. $C_{33}H_{44}O_4N_4Cl$ requires N, 9·4; Cl, 5·9%).

4-*Chlorocholesta*-1 : 4-*dien*-3-*one* (V) *and* 1 : 2-*Dichlorocholesta*-1 : 4-*dien*-3-*one* (VI).—Cholesta-1 : 4-dien-3-one (7 g.) in dimethylformamide (70 ml.) and dry ether (35 ml.) at −30° was treated with a 1·08M-solution of chlorine in propionic acid (17·8 ml.; 1·05 mol.). The chlorine was absorbed in 2 days at −30° in the dark. The product in light petroleum (b. p. 40—60°) was percolated through alumina (200 g.). Elution with light petroleum–benzene (7 : 3) gave 1 : 2-*dichlorocholesta*-1 : 4-*dien*-3-*one*, plates, m. p. 171—173°, $[\alpha]_D^{28}$ +23° (*c* 0·61), $\lambda_{max.}$ 258—259 mμ (4·05), ν 6·02 μ (Found: C, 71·8; H, 9·1; Cl, 15·6. $C_{27}H_{40}OCl_2$ requires C, 71·8; H, 8·9; Cl, 15·7%), after purification from methylene chloride–methanol. Further elution with light petroleum–benzene (1 : 1) gave 4-*chlorocholesta*-1 : 4-*dien*-3-*one*, needles, m. p. 129—131°, $[\alpha]_D^{24}$ +64° (*c* 0·46), $\lambda_{max.}$ 246 mμ (4·04), ν 6·02 μ (Found: C, 77·3; H, 10·0; Cl, 8·9. $C_{27}H_{41}OCl$ requires C, 77·8; H, 9·9; Cl, 8·5%), after crystallisation from methanol. Finally, elution with benzene–ether (1 : 1) gave cholesta-1 : 4-dien-3-one, m. p. and mixed m. p. 111—113°.

4-*Chlorocholesta*-1 : 4-*dien*-3-*one* 2 : 4-*dinitrophenylhydrazone* formed plates, m. p. 254—255° (decomp.), $\lambda_{max.}$ 396 mμ (4·55) (Found: N, 9·7; Cl, 6·6%), after purification from ethyl acetate–chloroform.

2ξ-*Bromo*-4ξ : 5ξ-*dichlorocholestan*-3-*one* (XI).—4ξ : 5ξ-Dichlorocholestan-3-one (4·1 g.) in methylene chloride (50 ml.) and acetic acid (100 ml.) was treated dropwise with a 1·088M-solution of bromine in acetic acid (8·5 ml.) in 5 min. Decolorisation was complete after a further 2 min., then the mixture was diluted with water. The methylene chloride layer was washed with water, dried (Na_2SO_4), and evaporated. 2ξ-*Bromo*-4ξ : 5ξ-*dichlorocholestan*-3-*one* crystallised from ethanol or ether–methanol in needles, m. p. 110—111°, $[\alpha]_D^{24}$ +86° (*c* 0·76) (Found: C, 60·0; H, 8·2; Hal, 27·4. $C_{27}H_{43}OCl_2Br$ requires C, 60·7; H, 8·1; Hal, 28·2%).

2ξ-*Bromo*-4-*chlorocholest*-4-*en*-3-*one* (X).—A solution of the foregoing compound (1 g.) in pyridine (20 ml.) was left at room temperature for 2 hr. The solution was poured into dilute sulphuric acid, and the product extracted with ether. 2ξ-*Bromo*-4-*chlorocholest*-4-*en*-3-*one* formed plates, m. p. 181—183°, $[\alpha]_D^{24}$ +90° (*c* 0·64), $\lambda_{max.}$ 260 mμ (4·01) (Found: C, 65·1; H, 8·7; Hal, 22·0. $C_{27}H_{42}OClBr$ requires C, 65·1; H, 8·5; Hal, 23·2%), after purification from hexane or ethanol.

Debromination of 2ξ-*Bromo*-4-*chlorocholest*-4-*en*-3-*one*.—The foregoing compound (250 mg.) in boiling methanol (10 ml.) and acetic acid (5 ml.) was treated with zinc dust (1 g.) for ½ hr. Isolation of the product with ether, and crystallisation from ethanol, gave 4-chlorocholest-4-en-3-one, needles, m. p. and mixed m. p. 125—126°.

Dehydrobromination of 2ξ-*Bromo*-4-*chlorocholest*-4-*en*-3-*one*.—(*a*) A solution of the 2ξ-bromo-derivative (1 g.) in collidine (10 ml.) was boiled under reflux under nitrogen for 45 min. The cooled mixture, on dilution with ether and filtration, afforded collidine hydrobromide (365 mg., 0·9 mol.). The product was decolorised by percolation in 4 : 1 light petroleum–benzene through alumina (10 g.), and crystallised from methanol to give 4-chlorocholesta-1 : 4-dien-3-one, needles, m. p. 130—131°, identical with the material prepared as above by direct chlorination of the dienone in dimethylformamide.

(*b*) The 2ξ-bromo-compound (5 g.) in dimethylformamide (50 ml.) containing lithium chloride (2 g.) was heated on the steam-bath for 4 hr., to give 4-chlorocholesta-1 : 4-dien-3-one, m. p. and mixed m. p. 129—131°.

Hydrogenation of 4-*Chlorocholesta*-1 : 4-*dien*-3-*one* (V).—The 4-chlorodienone (250 mg.) in methanol (200 ml.) was reduced in the presence of pre-reduced palladium–barium carbonate (20 mg.) until 1 mol. of hydrogen had been absorbed. The product in benzene–light petroleum (1 : 4) was chromatographed on alumina (4 g.). Elution with benzene–petroleum (1 : 1) gave 4-chlorocholest-4-en-3-one (60 mg.), m. p. 125—127°, $\lambda_{max.}$ 256 mμ (4·15), after crystallisation from ethanol.

Chlorination of 2-*Chlorocholesta*-1 : 4-*dien*-3-*one* (III).—A solution of the 2-chlorodienone (III) (1·3 g.) in ether (20 ml.) and dimethylformamide (20 ml.) at room temperature was treated with a 1·52M-solution of chlorine in propionic acid (2·25 ml.), and the mixture stored in the dark for 2 days. The product, after chromatography on alumina (40 g.), yielded 1 : 2-dichlorocholesta-1 : 4-dien-3-one, plates, m. p. and mixed m. p. 170—172°, with the sample prepared previously, $\lambda_{max.}$ 258 mμ (4·12).

The 4-chlorocholestadienone (V) resisted further chlorination.

Chlorination of Cholest-1-*en*-3-*one*.—A solution of cholest-1-en-3-one (2 g.) in ether (100 ml.) at −80° was treated with a 0·96M-solution of chlorine in propionic acid (6·5 ml., 1·03 mol.). After 6 hr. in the dark, the temperature of the mixture meanwhile rising to −30°, the chlorine-free solution was poured into ice-water. The ether was washed with ice-water and sodium hydrogen carbonate solution, dried, and evaporated at 0°. The oily residue failed to crystallise, but its solution in hexane began to evolve hydrogen chloride and subsequently afforded 2-chlorocholest-1-en-3-one, leaflets, m. p. and mixed m. p. 106—108°.

Chlorination of 2-*Chlorocholest*-1-*en*-3-*one* (IV).—The 2-chloro-compound (5 g.) in dry carbon tetrachloride (80 ml.) was treated at room temperature with a 0·935M-solution of chlorine in propionic acid (13·5 ml.). After 2 days the solution was washed with sodium hydrogen carbonate solution and water, and the solvent removed under reduced pressure. 1α : 2 : 2-*Trichlorocholestan*-3-*one* (XIII) separated from ethanol in flakes, m. p. 123—125°, $[\alpha]_D^{24}$ +78° (*c* 0·98), $\lambda_{max.}$ 296 mμ (ε 45) (in *cyclo*hexane) (Found: C, 66·0; H, 9·0; Cl, 22·4. $C_{27}H_{43}OCl_3$ requires C, 66·2; H, 8·5; Cl, 21·2%).

1 : 2-*Dichlorocholest*-1-*en*-3-*one* (XV).—A mixture of the 1α : 2 : 2-trichloride (1 g.), lithium chloride (100 mg.), and dimethylformamide (10 ml.) was heated under reflux for 30 min. The cooled solution was diluted with water and deposited 1 : 2-*dichlorocholest*-1-*en*-3-*one*, which after purification from ethanol formed blades, m. p. 153—156°, $[\alpha]_D^{25}$ +18° (*c* 0·26), $\lambda_{max.}$ 255 mμ

(4·16) (Found: C, 71·9; H, 9·4; Cl, 15·0. $C_{27}H_{42}OCl_2$ requires C, 71·5; H, 9·3; Cl, 15·6%). The 2 : 4-*dinitrophenylhydrazone* separated from chloroform–ethanol in orange flakes, m. p. 238—240°, $\lambda_{max.}$ 394 mμ (4·47) (in $CHCl_3$) (Found: Cl, 10·3. $C_{33}H_{46}O_4N_4Cl_2$ requires Cl, 11·2%).

Reaction between 1α : 2 : 2-*Trichlorocholestan-3-one and* o-*Phenylenediamine.*—The trichloride (1 g.), *o*-phenylenediamine (1 g.), and acetic acid (6 ml.) were boiled under reflux in nitrogen for 30 min., then poured into water. The product, isolated with chloroform, was percolated in benzene–light petroleum (1 : 1) through alumina (20 g.). The *quinoxaline derivative* (XIV) crystallised from ethanol in light brown flakes, m. p. 174—178°, $[\alpha]_D^{28}$ +205° (*c* 0·16), $\lambda_{max.}$ 225 (4·37), 243 (4·21), 264 (4·05), 311 (3·88), 325 (3·94), 340·5 (4·01) and 357 mμ (3·94) (Found: C, 78·9; H, 8·8; N, 5·3; Cl, 7·1. $C_{33}H_{47}N_2Cl$ requires C, 78·1; H, 9·3; N, 5·5; Cl, 7·0%).

Dehydrogenation of 1 : 2-*Dichlorocholest-1-en-3-one* (XV).—The 1 : 2-dichloro-compound (1·5 g.) was heated under reflux with selenium dioxide (0·5 g.) and acetic acid (0·2 ml.) in *tert.*-butyl alcohol (20 ml.) for 9 hr., then more selenium dioxide (0·5 g.) was added. After a further 8 hours' heating, half of the solvent was removed, and the residue allowed to cool. The solids were collected, washed with methanol, and percolated in benzene through alumina (2 g.). Purification from ethanol gave 1 : 2-dichlorocholesta-1 : 4-dien-3-one, m. p. 170—171°, $[\alpha]_D^{28}$ +25° (*c* 0·24), $\lambda_{max.}$ 258—259 mμ (4·05), identified by comparison of infrared spectra with the sample obtained by direct chlorination of the dienone in dimethylformamide.

1α : 2β-*Dichlorocholesta-4 : 6-dien-3-one* (XVIII).—Cholesta-1 : 4 : 6-trien-3-one (2 g.) in dry ether (50 ml.) at −30° was treated with a 1·27M-solution of chlorine in propionic acid (4·8 ml.) and kept at −30° in the dark for 40 hr. The *product*, crystallised from ethanol, then from hexane, formed needles, m. p. 100—102°, $[\alpha]_D^{23}$ −73° (*c* 0·40), $\lambda_{max.}$ 299 mμ (4·17), ν 6·02 μ (conjugated dienone) (Found: C, 74·1; H, 8·9; Cl, 15·2. $C_{27}H_{40}OCl_2$ requires C, 73·5; H, 9·1; Cl, 16·1%).

2-*Chlorocholesta-1 : 4 : 6-trien-3-one* (XIX).—A solution of the foregoing dichloride (850 mg.) in pyridine (5 ml.) was kept at 20—25° for 4 hr., then poured into dilute hydrochloric acid. 2-*Chlorocholesta-1 : 4 : 6-trien-3-one*, isolated by means of ether, formed prisms, m. p. 153—154°, $[\alpha]_D^{23}$ −45° (*c* 0·36), $\lambda_{max.}$ 217 (4·19), 268 (4·04), and 307 mμ (4·01) (Found: C, 77·7; H, 9·2; Cl, 9·6. $C_{27}H_{39}OCl$ requires C, 78·1; H, 9·5; Cl, 8·5%), after crystallisation from ethanol.

6β-*Bromo-2 : 2-dichlorocholest-4-en-3-one.*—(*a*) A solution of 6β-bromocholest-4-en-3-one (10 g.) in carbon tetrachloride (50 ml.) and acetic acid (50 ml.) was treated with a 1·27M-solution of chlorine in propionic acid (35·2 ml.) in the dark overnight. The separated leaflets were washed with hexane and purified from carbon tetrachloride–hexane, to give 6β-*bromo-2 : 2-dichlorocholest-4-en-3-one*, leaflets, m. p. 187—188°, $[\alpha]_D^{20}$ −30° (*c* 0·20), $\lambda_{max.}$ 256 mμ (4·11) (Found: C, 60·7; H, 7·6; Hal, 30·2. $C_{27}H_{41}OCl_2Br$ requires C, 60·9; H, 7·7; Hal, 28·3%).

(*b*) 5α : 6β-Dibromocholestan-3-one (5·44 g.) in carbon tetrachloride (50 ml.) and acetic acid (100 ml.) was treated with a 1·20M-solution of chlorine in propionic acid (17·1 ml.) in the dark for 24 hr. After being washed with water the solvent was removed under reduced pressure; crystallisation of the residue from acetone gave impure 5α : 6β-dibromo-2 : 2-dichlorocholestan-3-one, needles, m. p. 130—137°, $[\alpha]_D^{24}$ −3° (*c* 0·25), not fully transparent to ultraviolet radiation at 240—260 mμ. This material was dissolved in pyridine and after 1 hr. yielded 6β-bromo-2 : 2-dichlorocholest-4-en-3-one, m. p. and mixed m. p. 184—186° with the sample prepared as in (*a*).

Dehydrohalogenation of the foregoing compound (2 g.) with lithium chloride (1 g.) in dimethylformamide (30 ml.) at 100° for 1·5 hr. yielded 2-chlorocholesta-1 : 4 : 6-trien-3-one, m. p. 150—151°, mixed m. p. 150—153° with the sample prepared previously.

4-*Chlorocholesta-1 : 4 : 6-trien-3-one* (XVI).—A solution of cholesta-1 : 4 : 6-trien-3-one (3 g.) in dimethylformamide (50 ml.) was cooled to −30°, treated with a 1·095M-solution of chlorine in propionic acid (7·6 ml.) and stored in the dark at −30° for 16 hr. The product was purified by passage in benzene–light petroleum (1 : 1) through alumina (15 g.) and crystallisation from ethanol. 4-*Chlorocholesta-1 : 4 : 6-trien-3-one* formed needles, m. p. 115—116°, $[\alpha]_D^{25}$ +40° (*c* 0·75), $\lambda_{max.}$ 229 (4·10), 311 (3·85), $\lambda_{infl.}$ 258—260 mμ (3·86) (Found: C, 78·0; H, 9·3; Cl, 8·6. $C_{27}H_{39}OCl$ requires C, 78·1; H, 9·5; Cl, 8·5%).

6β-*Bromo-4-chlorocholest-4-en-3-one* (XXII).—A solution of 4-chlorocholest-4-en-3-one (5 g.) in ether (100 ml.) was cooled to 5° and treated dropwise with a 1·088M-solution of bromine in acetic acid (11·5 ml.). The reaction was complete in a few minutes, then the ether was evaporated under reduced pressure and the mixture diluted with methanol. The separated solids were washed with methanol and crystallised from ethanol. 6β-*Bromo-4-chlorocholest-4-en-3-one*

formed needles, m. p. 170—172°, $[\alpha]_D^{24}$ −136° (*c* 0·25), $\lambda_{max.}$ 266—267 mμ (4·06) (Found: C, 63·8; H, 8·7; Hal, 26·2. $C_{27}H_{42}OClBr$ requires C, 65·1; H, 8·5; Hal, 23·2%).

4-*Chlorocholesta*-4 : 6-*dien*-3-*one* (XXIII), prepared by heating the 6β-bromo-compound (1·5 g.) with lithium chloride (250 mg.) in dimethylformamide (12 ml.) under reflux for ½ hr., crystallised from ethanol in needles, m. p. 99—100°, $[\alpha]_D^{22}$ +57° (*c* 0·19), $\lambda_{max.}$ 298·5 mμ (4·27) (Found: C, 77·2; H, 9·6; Cl, 9·1. $C_{27}H_{41}OCl$ requires C, 77·7; H, 9·9; Cl, 8·5%). Its 2 : 4-*dinitrophenylhydrazone* formed plates, m. p. 271—273°, $\lambda_{max.}$ 397 mμ (4·58) with shoulders at 406 (4·57) and 414 mμ (4·54) (in $CHCl_3$) (Found: Cl, 6·1. $C_{33}H_{45}O_4N_4Cl$ requires Cl, 5·9%).

2α : 6β-*Dibromo*-4-*chlorocholest*-4-*en*-3-*one* (XX).—4-Chlorocholest-4-en-3-one (2 g.) in dry ether (50 ml.), cooled to 0°, was stirred and treated dropwise with a 0·97M-solution of bromine in acetic acid (10·0 ml.). Decolorisation was complete after 1 hr., then the ether was removed under reduced pressure. The crystalline solids were collected and purified from methylene chloride–methanol and finally from hexane, to give 2α : 6β-*dibromo*-4-*chlorocholest*-4-*en*-3-*one*, plates, m. p. 185—187°, $[\alpha]_D^{24}$ −105° (*c* 0·92), $\lambda_{max.}$ 270—271 mμ (4·05) (Found: C, 56·1; H, 7·1; Hal, 31·4. $C_{27}H_{41}OClBr_2$ requires C, 56·2; H, 7·2; Hal, 33·9%).

Dehydrobromination of 2α : 6β-*Dibromo*-4-*chlorocholest*-4-*en*-3-*one* (XX).—A solution of the 2α : 6β-dibromide (330 mg.) and lithium chloride (200 mg.) in dimethylformamide (10 ml.) was boiled under reflux under nitrogen for 1 hr., then cooled and poured into water. 4-Chlorocholesta-1 : 4 : 6-trien-3-one was obtained, having m. p. and mixed m. p. with a previous sample 113—115°, $[\alpha]_D^{25}$ +33° (*c* 0·30), $\lambda_{max.}$ 229 (4·10), 311 (4·08), $\lambda_{infl.}$ 260 mμ (3·85).

1α : 2β-*Dichloro*-17β-*propionoxyandrost*-4-*en*-3-*one* (II).—17β-Propionoxyandrosta-1 : 4-dien-3-one (2 g.) in dry ether (80 ml.) at −30° was treated with a 1·4M-solution of chlorine in propionic acid (4·4 ml.) and stored in the dark at −30° for 18 hr. 1α : 2β-*Dichloro*-17β-*propionoxyandrost*-4-*en*-3-*one* formed prisms, m. p. 141—144°, $[\alpha]_D^{26}$ +16° (*c* 1·23), $\lambda_{max.}$ 250 mμ (4·16) (Found: C, 63·4; H, 7·1; Cl, 16·4. $C_{22}H_{30}O_3Cl_2$ requires C, 63·9; H, 7·3; Cl, 17·1%).

2-*Chloro*-17β-*propionoxyandrosta*-1 : 4-*dien*-3-*one* (III), obtained when the foregoing 1α : 2β-dichloride (600 mg.) was treated with pyridine (3 ml.) for ½ hr., separated from methylene chloride–hexane in plates, m. p. 142—144°, $[\alpha]_D^{26}$ −4° (*c* 1·52), $\lambda_{max.}$ 251 mμ (4·21) (Found: C, 69·5; H, 7·8; Cl, 9·8. $C_{22}H_{30}O_3Cl$ requires C, 70·1; H, 7·8; Cl, 9·4%).

Chlorination of 17β-*Propionoxyandrosta*-1 : 4-*dien*-3-*one in Dimethylformamide*.—A solution of the dienone (2 g.) in dimethylformamide (30 ml.) was cooled in ice and treated with a 1·11M-solution of chlorine in propionic acid (5·3 ml.) in the dark for 4 hr. The product was chromatographed in light petroleum (b. p. 40—60°) on alumina (50 g.). Elution with light petroleum–benzene (3 : 1) gave 1 : 2-*dichloro*-17β-*propionoxyandrosta*-1 : 4-*dien*-3-*one* (VI), flakes, m. p. 235—237°, $[\alpha]_D^{24}$ +40° (*c* 1·19), $\lambda_{max.}$ 257·5 mμ (4·10) (Found: C, 64·1; H, 7·1; Cl, 15·3. $C_{22}H_{28}O_3Cl_2$ requires C, 64·2; H, 6·9; Cl, 17·2%), after crystallisation from methylene chloride–hexane. Elution with benzene furnished 4-*chloro*-17β-*propionoxyandrosta*-1 : 4-*dien*-3-*one* (V) which separated from aqueous methanol in leaflets, m. p. 138—141°, $[\alpha]_D^{23}$ +76° (*c* 1·28), $\lambda_{max.}$ 246 mμ (4·05) (Found: C, 69·9; H, 7·5; Cl, 9·5. $C_{22}H_{29}OCl_3$ requires C, 70·1; H, 7·8; Cl, 9·4%). Continued elution with benzene and benzene–ether (4 : 1) gave some unchanged dienone, m. p. 128—130°.

2ξ-*Bromo*-4ξ : 5ξ-*dichloro*-17β-*propionoxyandrostan*-3-*one* (XI).—A 0·204M-solution of bromine in acetic acid (47·5 ml.) was added dropwise to 4ξ : 5ξ-dichloro-17β-propionoxyandrostan-3-one (4 g.) in acetic acid (60 ml.). Decolorisation was complete in 5 min., then the mixture was poured into water. 2ξ-*Bromo*-4ξ : 5ξ-*dichloro*-17β-*propionoxyandrostan*-3-*one* formed prisms, m. p. 160—163°, $[\alpha]_D^{27}$ +67° (*c* 0·86) (Found: C, 53·6; H, 6·5; Hal, 29·2. $C_{22}H_{31}O_3Cl_2Br$ requires C, 53·5; H, 6·3; Hal, 30·5%), after purification from acetone–hexane.

2ξ-*Bromo*-4-*chloro*-17β-*propionoxyandrost*-4-*en*-3-*one* (X), prepared by treating the foregoing compound (2 g.) with pyridine (10 ml.) at room temperature for 1 hr., crystallised from methylene chloride–methanol in plates, m. p. 181—183°, $[\alpha]_D^{27}$ +61° (*c* 1·10), $\lambda_{max.}$ 260 mμ (4·08) (Found: C, 58·7; H, 6·7; Hal, 23·2. $C_{22}H_{30}O_3ClBr$ requires C, 57·7; H, 6·6; Hal, 25·2%). This compound (5 g.) with lithium chloride (2 g.) in dimethylformamide (50 ml.) on the steam-bath for 4 hr., or in collidine (6 vols.) under reflux under nitrogen gave 4-chloro-17β-propionoxyandrosta-1 : 4-dien-3-one, m. p. and mixed m. p. 140—141°.

1α : 2β-*Dichloro*-17β-*propionoxyandrosta*-4 : 6-*dien*-3-*one* (XVIII).—17β-Propionoxyandrosta-1 : 4 : 6-trien-3-one (2 g.) in dry ether (70 ml.) at −30° was treated with a 1·16M-solution of chlorine in propionic acid (5·3 ml.) at −30° in the dark for 20 hr. The *product* separated from methylene chloride–methanol in needles, m. p. 134—135°, $[\alpha]_D^{20}$ −172° (*c* 0·43),

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$\lambda_{max.}$ 296·5 mμ (4·36) (Found: C, 64·3; H, 7·0; Cl, 18·0. $C_{22}H_{28}O_3Cl_2$ requires C, 64·3; H, 6·9; Cl, 17·2%).

2-*Chloro*-17β-*propionoxyandrosta*-1 : 4 : 6-*trien*-3-*one* (XIX), prepared by keeping a solution of the preceding dichloride (1·2 g.) in pyridine (5 ml.) at 30° for 15 min., formed needles, m. p. 140—141°, $[\alpha]_D^{25}$ −7° (*c* 0·57), $\lambda_{max.}$ <220, 267·5 (4·04), and 305 mμ (4·01) (Found: C, 70·6; H, 7·5; Cl, 9·4. $C_{22}H_{27}O_3Cl$ requires C, 70·5; H, 7·3; Cl, 9·2%), after crystallisation from hexane.

4-*Chloro*-17β-*propionoxyandrosta*-1 : 4 : 6-*trien*-3-*one* (XVI).—(*a*) A solution of the trienone (XIV) (2·5 g.) in dry ether (25 ml.) and dimethylformamide (25 ml.) at −30° was treated with a 0·99M-solution of chlorine in propionic acid (7·5 ml.) for 16 hr. in the dark. The product in benzene was percolated through alumina (15 g.), to give 4-*chloro*-17β-*propionoxyandrosta*-1 : 4 : 6-*trien*-3-*one*, square plates, m. p. 97—100°, $[\alpha]_D^{24}$ +44° (*c* 0·49), $\lambda_{max.}$ 229 (4·12) and 310·5 mμ (4·11), $\lambda_{infl.}$ 255 mμ (3·85) (Found: C, 69·8; H, 7·5; Cl, 9·8. $C_{22}H_{27}O_3Cl$ requires C, 70·5; H, 7·3; Cl, 9·5%), after crystallisation from hexane.

(*b*) 4-Chloro-17β-propionoxyandrost-4-en-3-one (10 g.) in dry ether (400 ml.) was treated with a 1·04M-solution of bromine in propionic acid (52 ml.), dropwise at room temperature. A drop of 50% solution of hydrogen bromide in acetic acid was added to initiate the reaction, decolorisation being complete in 3 hr. The solution was diluted with light petroleum (b. p. 40—60°) to turbidity, and cooled in ice. The crystalline solids were collected, washed with light petroleum, and purified from methylene chloride–hexane. 2α : 6β-*Dibromo*-4-*chloro*-17β-*propionoxyandrost*-4-*en*-3-*one* (XX) formed flakes, m. p. 197—199°, $[\alpha]_D^{24}$ −123° (*c* 1·77), $\lambda_{max.}$ 270 mμ (4·08).

The 2α : 6β-dibromide (2·5 g.) in dimethylformamide (25 ml.) containing lithium chloride (1 g.) was boiled under reflux under nitrogen for 1 hr., to give 4-chloro-17β-propionoxyandrosta-1 : 4 : 6-trien-3-one, m. p. and mixed m. p. 98—100° with a sample prepared as in (*a*).

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., LONDON, N.1. [*Received, November 19th*, 1957.]

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270. *The Chemical Synthesis of Polysaccharides. Part II.* The Chemical Synthesis of Nigerose.*

By S. HAQ and W. J. WHELAN.

Nigerose (3-*O*-α-D-glucopyranosyl-D-glucose) has been synthesised by reaction between 3 : 4 : 6-tri-*O*-acetyl-1-chloro-β-D-glucopyranose and 1 : 2-5 : 6-di-*O*-*iso*propylidene-3-*O*-sodio-α-D-glucofuranose. Minor products are kojibiose, a trehalose, and an unidentified diglucose.

THE chemical synthesis of *O*-α-D-glucopyranosyl-(1 ⟶ 3)-D-glucose was achieved in 1946 by Gakhokidze,[1] by treatment of a mixture of 4 : 6-*O*-benzylidene-1 : 2-*O*-*iso*propylidene-α-D-glucopyranose and 2 : 3 : 4 : 6-tetra-*O*-acetyl-D-glucose with zinc chloride and phosphoric oxide. The properties of the sugar and a crystalline acetyl derivative were recorded. The isolation of the disaccharide was not reported again until 1953, when Barker, Bourne, and Stacey [2] obtained it from a partial hydrolysate of the fungal polysaccharide nigeran, and gave it the name nigerose. The structure was established [2] by conversion of the sugar into the same osazone as is formed by turanose (3-*O*-α-D-glucopyranosyl-D-fructose), and the crystalline β-octa-*O*-acetyl derivative [3] has been used to characterise the sugar. Recently Barker, Bourne, O'Mant, and Stacey [4] provided further

* Part I, *J.*, 1956, 4543.

[1] Gakhokidze, quoted by Evans, Reynolds, and Talley, *Adv. Carbohydrate Chem.*, 1951, **6**, 27; see also *J. Gen. Chem. U.S.S.R.*, 1949, **19**, 2100; *Chem. Abs.*, 1950, **44**, 3913.
[2] Barker, Bourne, and Stacey, *J.*, 1953, 3084.
[3] Peat, Whelan, and Hinson, *Chem. and Ind.*, 1955, 385.
[4] Barker, Bourne, O'Mant, and Stacey, *J.*, 1957, 2448.

structural evidence by means of methylation analysis. After the isolation from nigeran, nigerose was obtained from a variety of sources (see Table). With two exceptions all these specimens and their acetyl derivatives have the same specific optical rotations as the material from nigeran and these values are very different from those reported by Gakhokidze.[1] The exceptions are specimens of the free sugar synthesised by Pazur and his co-workers [5,6] who effected the acid- and enzyme-catalysed transfer of a glucose unit from maltose to glucose. Their products had the same $[\alpha]_D$ as Gakhokidze's specimen and gave turanosazone on treatment with phenylhydrazine, but the acetyl derivatives were not prepared. Despite the many reports of the isolation of nigerose the only definitive chemical synthesis has been that by Gakhokidze. We have resolved the conflict by a chemical synthesis of 3-*O*-α-D-glucopyranosyl-D-glucose.

The desired linkage has the α-configuration. The synthesis of α-glucosidic disaccharides is difficult and it is only in the last few years that sucrose,[7] maltose,[8] αα-trehalose,[9] and kojibiose [10] (2-*O*-α-D-glucopyranosyl-D-glucose) have been chemically synthesised, though always in yields of only a few per cent. In each case the compound used to form the α-glucosyl group in the disaccharide was 3 : 4 : 6-tri-*O*-acetyl-1 : 2-anhydro-α-D-glucopyranose (Brigl's anhydride [11]). β-Linked disaccharides are usually synthesised by the Koenigs–Knorr reaction but for the synthesis of an α-diglucose by this method a tetra-*O*-acetyl-β-halogenoglucose would be required and the known examples of this type are unstable. However, 3 : 4 : 6-tri-*O*-acetyl-1-chloro-β-D-glucopyranose [12] is reasonably stable and was chosen in preference to Brigl's anhydride since it allowed the use of the 3-*O*-sodio-derivative of the second reactant, 1 : 2-5 : 6-di-*O*-*iso*propylidene-α-D-glucofuranose, in the attempt to increase the reactivity of the 3-hydroxyl group. This group is rather unreactive, as can be seen by comparing the yields of gentiobiose [12] (74%; β-1 : 6-linked diglucose) and laminaribiose (9·5%,[13] *ca.* 2%,[14] β-1 : 3-linked diglucose) obtained by the Koenigs–Knorr reaction. The ultimate yield of nigerose (see below) was not, however, greater than the yields of disaccharides synthesised from Brigl's anhydride. Competition was expected from self-condensation of the halogenoglucose through its free 2-hydroxyl group, forming kojibiose,[10,15] and this, in fact, happened (see below).

The two reactants were refluxed in toluene, conditions used by Gilbert, Smith, and Stacey [16] in a similar type of condensation with di*iso*propylidenesodioglucose. The products were deacetylated and fractionated on charcoal–Celite into free sugars and *iso*propylidene derivatives. It had been hoped to obtain a di-*O*-*iso*propylidene derivative of nigerose but the isolation of 1 : 2-*O*-*iso*propylidene-D-glucose showed that some loss of acetone had taken place. (When synthesising laminaribiose from acetobromoglucose and di*iso*propylideneglucose, Freudenberg and Oertzen [14] encountered the same behaviour, some 40% of the di*iso*propylideneglucose being decomposed into the mono*iso*propylidene derivative.) The acetone residues were therefore removed with acid from the mixed derivatives of glucose and nigerose, and 231 mg. (1·8%) of chromatographically pure disaccharide were finally obtained. Much more nigerose was undoubtedly present, but it proved impossible preferentially to hydrolyse the *iso*propylidene residues without severing the inter-sugar linkage, either under the conditions chosen or those described by

[5] Pazur and Budovich, *J. Amer. Chem. Soc.*, 1956, **78**, 1885.
[6] Pazur, Budovich, and Tipton, *ibid.*, 1957, **79**, 625.
[7] Lemieux, *Canad. J. Chem.*, 1953, **31**, 949.
[8] Lemieux and Huber, *J. Amer. Chem. Soc.*, 1956, **78**, 4117.
[9] Lemieux and Bauer, *Canad. J. Chem.*, 1954, **32**, 340.
[10] Haq and Whelan, *Nature*, 1956, **178**, 1221.
[11] Brigl, *Z. physiol. Chem.*, 1921, **116**, 1.
[12] Reynolds and Evans, *J. Amer. Chem. Soc.*, 1938, **60**, 2559.
[13] Bächli and Percival, *J.*, 1952, 1243.
[14] Freudenberg and Oertzen, *Annalen*, 1951, **574**, 37.
[15] Barker, Bourne, Grant, and Stacey, *Nature*, 1956, **178**, 1221.
[16] Gilbert, Smith, and Stacey, *J.*, 1946, 622.

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Freudenberg and Oertzen [14] and Bächli and Percival [13] for the hydrolysis of the corresponding derivatives of laminaribiose.

Properties of nigerose, nigerosazone and β-nigerose octa-O-acetate obtained from various sources.

Source	Nigerose, $[\alpha]_D$ in H_2O	Nigerosazone, m. p.	β-Nigerose octa-*O*-acetate m. p.	$[\alpha]_D$ in $CHCl_3$	Ref.
Present work	135°	—	151—152°	84°	—
Nigeran	136	204—206°	149—150	72	2, *a*
Amylopectin	—	—	151—153	80	*b*
*iso*Lichenin	138·8	—	149	84·9	*c*
Floridean starch	136·9	—	147—148	86·6	*d*
Acid + glucose	—	—	155—157 *	78	*e*
Aspergillus niger enzyme + glucose	134	—	151—152	75	3
Schizosaccharomyces pombe enzyme + glucose	—	—	150—150·5	—	
Koji extract + glucose	135	205	150	80	*g*
Chemical synthesis (Gakhokidze)	84·8	—	149	41·3	1
Acid + glucose + maltose	87	205—206	—	—	5
Aspergillus oryzae enzyme + glucose + maltose	89	204—205	—	—	6

* Corr.

(*a*) Barker, Bourne, and O'Mant, *Chem. and Ind.*, 1955, 425; (*b*) Wolfrom and Thompson, *J. Amer. Chem. Soc.*, 1956, **78**, 4116; (*c*) Morgan, Ph.D. Thesis, Wales, 1956; (*d*) Peat, Turvey, and Evans, *Nature*, 1957, **179**, 261; (*e*) Thompson, Anno, Wolfrom, and Inatome, *J. Amer. Chem. Soc.*, 1954, **76**, 1309; (*f*) Shibasaki, *Tohôku J. Agric. Res.*, 1955, **6**, 171; (*g*) Matsudo and Aso, *ibid.*, 1954, **5**, 123.

Properties of Synthetic Nigerose.—The synthetic disaccharide had $[\alpha]_D$ 145° (in H_2O) and formed a crystalline β-acetyl derivative having the same properties as all other such preparations, except that obtained by Gakhokidze [1] (see Table). The sugar obtained by deacetylation of the acetate had $[\alpha]_D$ 135°. Again this is in line with all reported values except those of Gakhokidze and Pazur *et al.* The somewhat higher value of $[\alpha]_D$ of the whole synthetic preparation suggested that it was not completely pure, although paper chromatography and ionophoresis revealed only one component, having the same behaviour as a sample of nigerose from *iso*lichenin.[17]

It is therefore confirmed that the sugar isolated from nigeran by Barker *et al.*[2] and having the same properties as samples isolated by all later workers except Pazur *et al.* (see Table) is 3-*O*-α-D-glucopyranosyl-D-glucose. The fact that Pazur *et al.* obtained turanosazone from their preparations suggests that nigerose was present but it must have been impure. This might explain Gakhokidze's findings but the properties of his acetyl derivative are unlike those of any known octa-*O*-acetyl derivative of a glucose disaccharide and the magnitude of its $[\alpha]_D$ excludes the possibility that this was the unknown α-nigerose octa-*O*-acetate.

Minor Products of the Reaction.—There were three other disaccharide products of the condensation reaction. One, kojibiose (50 mg.), was found uncombined with acetone, indicating that it arose solely from the reaction between two molecules of 3 : 4 : 6-tri-*O*-acetyl-1-chloro-β-D-glucose, as already mentioned. The second was a trehalose (73 mg.), probably the αα-isomer; this was also formed along with kojibiose when Brigl's anhydride was polymerised.[10] The third product (*X*) (46 mg.) had the same R_F value as isomaltose and gentiobiose and its $[\alpha]_D$ value (83°) suggested that it might be a mixture of the two sugars ($[\alpha]_D$ 122° and 9·6°, respectively) but the properties of its crystalline β-octa-*O*-acetate (m. p. 192°; $[\alpha]_D$ 30°) distinguish it from any known diglucose acetate. It may perhaps be 5-*O*-α-glucosylglucose, which has not yet been described. This could be formed by reaction between the chloroglucose and the 5-hydroxyl group of 1 : 2-*O*-*iso*propylideneglucose, shown to be a by-product of the reaction.

[17] Morgan, Ph.D. Thesis, Wales, 1956.

Experimental

3 : 4 : 6-*Tri*-O-*acetyl*-1-*chloro*-β-D-*glucopyranose*.—This was prepared from β-glucose penta-*O*-acetate by Brigl's method,[11] as modified by Lemieux and Huber.[18] It had m. p. 157—158° (lit.,[11] m. p. 158°).

1 : 2-5 : 6-*Di*-O-iso*propylidene*-3-O-*sodio*-D-*glucofuranose*.—1 : 2-5 : 6-Di-*O*-*iso*propylidene-D-glucofuranose (10 g.) was treated with sodium (0·88 g., 1 mol.), as by Gilbert *et al.*,[16] in the apparatus designed by Philip, Scherer, and Field.[19]

Synthesis of Nigerose.—The 3-sodio-compound from 10 g. of sugar (as above) was dissolved in sodium-dried toluene (50 ml.), and the chloroglucose (14·5 g.) was added, some of which did not at first dissolve. After 48 hours' shaking at room temperature a sample gave a positive test for chloride and, tested on treatment with alkali (deacetylation) and then with hot dilute sulphuric acid (removal of acetone), followed by paper chromatography, gave a faint disaccharide spot but there was much unchanged glucose. Accordingly the solution was heated under reflux for 11 days, during which it became dark brown. The cooled mixture was filtered and evaporated. The residue was dissolved in a 0·5N-solution of sodium hydroxide in 50% acetone (200 ml.) and kept at 0° for 48 hr. After neutralisation with 3N-sulphuric acid the solution was applied to a charcoal–Celite column (150 × 5 cm.; equal parts by weight of B.D.H. " activated charcoal " and Celite No. 535) which was eluted by the gradient method.[20] A reservoir of water (10 l.) was connected to the top of the column, about 6 ft. below, and the level in this reservoir was automatically maintained by feeding in 60% aqueous ethanol with stirring. The fractions (150—200 ml. each) were collected automatically and after passage through a Seitz filter their optical rotations (4 dm. tube) were measured. Paper chromatography was also used as a guide to the identity of the substances. Each fraction was examined before and after treatment with 0·01N-sulphuric acid at 100° for 5 min. *iso*Propylidene derivatives were rendered visible by spraying the chromatogram with 10% trichloroacetic acid and heating it for 15 min. at 100° to remove the *iso*propylidene groups before spraying with benzidine–trichloroacetic acid.[21] Fractions 1—22 (1·2 g.) contained glucose; fractions 23—36 (2·13 g.) contained kojibiose (see below); fractions 37—98 (3·5 g.) contained mono- and di-*iso*propylideneglucose and a substance migrating between these compounds. Acid hydrolysis of this mixture gave glucose and nigerose. When fraction 98 had been collected the column was eluted with ethanol (2 l.), which removed 1·3 g. of carbohydrate. This was combined with fractions 37—98 and attempts were made preferentially to remove *iso*propylideneglucoses by extraction with solvents. The ethanolic extract deposited 1 : 2-*O*-*iso*propylideneglucose, which after several recrystallisations from methanol had m. p. 160° and $[\alpha]_D$ −11·2° (in EtOH; *c* 0·22) (lit.,[22] m. p. 161—162·5°, $[\alpha]_D$ −11·8°). The remaining material (4·7 g.) was heated in 0·01N-sulphuric acid (30 ml.) at 100° for 15 min. The solution was neutralised by aqueous sodium hydroxide and adsorbed on charcoal–Celite (100 × 3·5 cm.), and glucose was eluted with water. 7·5% Ethanol (1·8 l.) was then applied and the optically active material obtained was combined and evaporated. The residue (549 mg.) was found by chromatography to contain nigerose, a reducing sugar moving slightly faster than glucose, and mono*iso*propylideneglucose. These were separated by chromatography on six sheets of thick filter paper in butan-1-ol–acetic acid–water (4 : 1 : 5) into nigerose (67 mg.), reducing sugar (33 mg.), and mono*iso*propylideneglucose (289 mg.). The charcoal column was then eluted with 80% ethanol (3 l.), and 2·78 g. of carbohydrate were obtained. It was evident that hydrolysis of the *iso*propylidene derivatives was far from complete. Accordingly the 80% ethanol extract was heated in 0·015N-sulphuric acid at 100° for 35 min. After neutralisation and fractionation on charcoal–Celite (66 × 2·5 cm.) as before, the 7·5% ethanol extract (0·383 g.) contained a sugar (*X*) moving with isomaltose (and gentiobiose), along with nigerose and a trace of glucose. Fractionation on thick filter paper (5 sheets) gave *X* (46 mg.) and nigerose (164 mg.). The total yield of nigerose was therefore 231 mg. (1·8% based on the di*iso*propylideneglucose).

Characterisation of Nigerose.—On paper chromatography and paper ionophoresis in borate

[18] Lemieux and Huber, *Canad. J. Chem.*, 1953, **31**, 1040.
[19] Philip, Scherer, and Field, *Rayon Textile Monthly*, Oct., 1941, p. 51.
[20] Alm, *Acta Chem. Scand.*, 1952, **6**, 1186; Bacon and Bell, *J.*, 1953, 2528.
[21] Bacon and Edelman, *Biochem. J.*, 1951, **48**, 114.
[22] Fischer and Rund, *Ber.*, 1916, **49**, 93.

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buffer (pH 8·7), with spray reagents to detect reducing and non-reducing sugars,[23] nigerose behaved as a single component, having the same R_F and M_G values as a sample from *iso*lichenin.[17]

Nigerose (90 mg.) was acetylated with sodium acetate–acetic anhydride, and the product was worked up in the usual way, the chloroform-soluble syrup (125 mg.) depositing crystals (from ethanol), m. p. 147—148°, which after two further crystallisations melted at 151—152° and had $[\alpha]_D$ +84° (in $CHCl_3$; *c* 0·42) (Found: C, 49·8; H, 5·9. Calc. for $C_{28}H_{38}O_{19}$: C, 49·6; H, 5·6%). The mixed m. p. with β-nigerose octa-*O*-acetate obtained from *iso*lichenin [17] (see Table) was 150°. The acetate (8·39 mg.) was dissolved in dry methanol saturated with ammonia (2 ml.) and left for 2 hr. at room temperature. The ammonia and methanol were then removed by storage over concentrated sulphuric acid and solid potassium hydroxide. The residue was dissolved in water (5 ml.) and α_D (1 dm. tube) was measured (0·114°). The free sugar therefore had $[\alpha]_D$ +135° (*c* 0·08). The specific optical rotation of the original sugar, based on determination of concentration by acid hydrolysis to glucose,[24] was +145° (*c* 0·05; 4 dm. tube).

Minor Disaccharide Products Formed during the Synthesis of Nigerose.—(a) *Kojibiose and trehalose.* Fractions 23—36 (2·13 g.; see above), obtained during the first fractionation of the reaction mixture, contained a disaccharide together with traces of trisaccharide and mono*iso*propylideneglucose. The fraction was adsorbed on charcoal–Celite (100 × 2·6 cm.) which was eluted with water and then 7·5% ethanol to remove the disaccharide (732 mg.). To ensure freedom from nigerose and *X* (see below) the material was fractionated by ionophoresis [23] on three sheets of thick filter paper (18½ × 22½ in.) in 0·02M-borate buffer (pH 8·7) for 16 hr. with an applied potential of 9 v/cm. The main disaccharide component was eluted with water; the pH was adjusted to 5 with hydrochloric acid and the sodium borate removed on charcoal.[22] The disaccharide fraction (275 mg.) had the same R_F and M_G values as authentic kojibiose [10, 15] and likewise failed to react on paper with triphenyltetrazolium chloride spray reagent. A test was made for the presence of αα-trehalose, which had been formed with kojibiose in the synthesis of this sugar from Brigl's anhydride.[10] The two sugars have the same R_F value. The kojibiose was destroyed by heating the sugar with 0·4N-barium hydroxide for 3 hr. at 100°. After neutralisation with sulphuric acid, paper chromatography showed a non-reducing sugar to be present in the position previously occupied by kojibiose. The sugars were separated by converting the kojibiose into the methyl furanoside, following the general procedure described by Barker, Bourne, and O'Mant.[25] The fraction (240 mg.) was dissolved in 4% (w/w) methanolic hydrogen chloride and stored at room temperature. The optical rotation (1 dm. tube) became constant after 4 hr. (1·13° ⟶ 0·99°). Freshly prepared silver carbonate (7 g.) was added and, when neutral, the mixture was centrifuged, the solid was washed with methanol, and the combined solutions were evaporated over freshly washed and dried barium carbonate. 80% Aqueous methanol extracted from this residue a product (584 mg.) still containing some silver salts. This was fractionated on four sheets of thick filter paper and the zones corresponding to the two non-reducing disaccharide components, trehalose (73 mg.) and methyl kojibioside (R_F equal to that of glucose; 157 mg.) were eluted and evaporated. The furanoside was dissolved in 0·01N-hydrochloric acid (156 ml.), and stored at 42—48°. Samples were removed at intervals, neutralised with silver carbonate, and examined by chromatography. At 64 hr. the methyl furanoside had disappeared and was replaced by the benzidine-reducing disaccharide. After 72 hr. the whole solution was neutralised and worked up as before. The product contained a trace of glucose which was removed by chromatographic fractionation on thick filter paper. The final product weighed 50 mg. The chromatographic and ionophoretic properties and the infrared spectrum were identical with those of kojibiose.[15]

(b) *Disaccharide* X. This was obtained when the synthetic *iso*propylidenedisaccharides were hydrolysed with 0·015N-sulphuric acid (see above). It had the same R_F and M_G values as isomaltose but had $[\alpha]_D$ +83° (in H_2O; *c* 0·03) and with sodium acetate–acetic anhydride gave an acetate, m. p. 192°, $[\alpha]_D$ +30° (in $CHCl_3$; *c* 0·07).

We thank the Pakistan Council of Scientific and Industrial Research and the Colombo Plan Authority for the Award of a grant (to S. H.).

THE LISTER INSTITUTE, LONDON, S.W.1. [*Received, December 4th*, 1957.]

[23] Peat, Whelan, and Roberts, *J.*, 1957, 3916.
[24] Pirt and Whelan, *J. Sci. Food Agric.*, 1951, **2**, 224.
[25] Barker, Bourne, and O'Mant, *Chem. and Ind.*, 1955, 425.

271. *First-order Calculation of Factor Group Splittings in the Electronic Spectra of Durene, Ovalene, and Phthalocyanine Crystals.*

By L. E. Lyons.

Certain characteristics of crystal spectra of durene, ovalene, and phthalocyanine are predicted by first-order theory, using known *X*-ray crystal structures and the extinction coefficients of solutions.

Calculation of factor group splittings has followed Davydov's application [1] of Frenkel's exciton ideas.[2] Two methods have been used: (i) intermolecular integrals have been expressed in terms of transition-moment integrals which were then evaluated from experimental observations; and (ii) intermolecular integrals have been calculated from theory, after assumption of explicit forms for the molecular wave functions. Method (i) was worked out by Davydov and was used for calculations on anthracene [3] and naphthalene.[4] Method (ii) has been fully worked out for benzene by Fox and Schnepp.[5] Of the two methods, (i) is easier to apply, since (ii) becomes cumbersome for large molecules. Since the method involves a multipole expansion of intermolecular interactions, the expansion is not accurate when the interacting molecules are separated by distances comparable with molecular dimensions. However, by its use Bree and Lyons [6] have accounted almost quantitatively for the intensity of light absorption by an anthracene crystal and at least semiquantitatively for the splitting. In this paper integrals are calculated to the first-order for several crystals of $P2_1/a$ symmetry. Since the polarization of most of the electronic transitions in these molecules is not known the values of integrals and splittings are calculated for both in-plane directions, l (longer) and m (shorter). Second-order effects [7] are very important when considering polarization ratios but produce only a relatively small alteration in the splitting.[7,8] Winston's criticism [9] of the original theory [1] does not apply to the procedure [3] here followed. A further criticism of the summation procedure has been answered [10] previously. In each crystal there are two molecules to the unit cell.[11] It follows that there will be two sets of electronic energy levels for each non-degenerate level in the isolated molecule. If allowed transitions are considered, then only one level of each set (with the excitation wave vector $K = 0$) need be considered. The energy difference between these levels, α and β, is the splitting, given [3] by:

$$E_\alpha - E_\beta = 2\sum_j I_{oj} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where j denotes a molecule translationally equivalent to the unit cell partner of molecule o, and

$$I_{oj} \equiv \int \phi'_o \phi_j V_{oj} \phi_o \phi'_j \, dv$$

ϕ_o, ϕ'_j being ground- and excited-state molecular wave functions and V_{oj} the operator for the interaction between o and j, which may be expanded as a multipole series. In the expansion the dipole–dipole term is retained and the others assumed negligible, so that:

$$I_{oj} = [e^2/r_{oj}^3] F_{l(m)} \cdot \int \phi'_o (\sum_p \rho_p) \phi_j \, dv \int \phi'_j (\sum_q \rho_q) \phi_o \, dv \quad . \quad . \quad . \quad . \quad (2)$$

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[1] Davydov, *Zhur. eksp. teor. Fiz.*, 1948, **18**, 210.
[2] Frenkel, *Phys. Rev.*, 1931, **37**, 17.
[3] Craig and Hobbins, *J.*, 1955, 539.
[4] Craig and Walsh, *J. Chem. Phys.*, 1956, **24**, 471.
[5] Fox and Schnepp, *ibid.*, 1955, **23**, 767.
[6] Bree and Lyons, *J.*, 1956, 2662.
[7] Craig, *J.*, 1955, 2302.
[8] McClure and Schnepp, *J. Chem. Phys.*, 1955, **23**, 1575.
[9] Winston, *ibid.*, 1951, **19**, 156.
[10] Craig and Walsh, *ibid.*, 1956, **25**, 588.
[11] Robertson, *Proc. Roy. Soc.*, 1933, *A*, **142**, 659; Donaldson and Robertson, *ibid.*, 1953, *A*, **220**, 157; Robertson and Woodward, *J.*, 1937, 219.

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where $F_{l(m)}$ is the "angle factor" for a long (short) axis transition given by

$$F_l = 2lz \,.\, lz' - lx \,.\, lx' - ly \,.\, ly' \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

In (3) lz (or lz') denotes the cosine of the angle, $\angle lz$, between the molecular direction l (or l') and z, the intermolecular line drawn from l to j; $\rho_{p(q)}$ denotes the co-ordinate of electron $p(q)$ in molecule o(j). The integrals in equation (2) are the usual transition dipole-moment integrals, M, of absorption spectroscopy. Reference directions in the crystal are such that d is perpendicular to both the a and b crystal directions. The x direction is drawn perpendicular to z in the (001) plane from the centre of molecule j; y is perpendicular to both x and z. Directions within molecule o are indicated by l, m, and n, all mutually perpendicular; in molecule j by l', m', and n'. The matrix $(l'a)$ is defined as:

$$(l'a) = \begin{pmatrix} l'a & l'b & l'd \\ m'a & m'b & m'd \\ n'a & n'b & n'd \end{pmatrix}$$

From the symmetry of the crystal,

$$(l'a) = (la) \,.\, \begin{pmatrix} -1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & -1 \end{pmatrix}$$

Also, $(lx) = (la) \,.\, (ax)$, and $(l'x) = (l'a) \,.\, (ax)$.
By means of these relations it may be shown that:

$$F_l = lb^2(2bz^2 - bx^2 - by^2) - la^2(2az^2 - ax^2 - ay^2) - ld^2(2dz^2 - dx^2 - dy^2) - 2la \,.\, ld\,(2az \,.\, dz - aydy - ax \,.\, dx) \quad . \quad (4)$$

where lb^2 denotes $\cos^2 \angle lb$; etc.

A similar expression holds for F_m.

For molecules in the same (001) plane, equation (4) simplifies to

$$F_l = lb^2(2 \sin^2 \angle az - az^2) - la^2(az^2 - \sin^2 \angle az) + ld^2 \quad . \quad . \quad . \quad (5)$$

For two molecules in the same (001) plane it is necessary to evaluate interactions only for one quadrant; for molecules in different planes interactions over a half-plane must be calculated. The remainder follow by symmetry. With reference to molecule o, other non-equivalent sites are designated as in Fig. 1. A prime indicates the corresponding molecule in the adjacent plane (*e.g.*, C′ and C).

FIG. 1. *Designation of sites in* (001) *plane.*

The molecules are so labelled that F′ lies nearer to o than does C′. Calculations were made for all molecule pairs for which $r_{oj} < 20$ Å.

The values calculated for $[e^2/r_{ij}^3]F_{l(m)}$ are given for various molecule pairs in Tables 1 and 2. The unit of cm.$^{-1}$ Å^{-2} is convenient if M, the transition-moment integral, is expressed in Å. For $M = 1$, the sum of the interactions between inequivalent molecules in the same (001) plane is given by $4\sum$; in the two adjacent planes, one above and one below, by $4\sum'$. Thus the total interaction is $4(\sum + \sum')$.

Values of $4(\sum + \sum')$ for anthracene were calculated by the formulæ used for the other substances, as l 1737; m 144. Craig and Walsh [10] obtained 1796 and 152; the slight discrepancy arises because the sign of az is taken differently for molecule pairs such as oF′.

Since $\sum_j I_{oj} = 4(\sum + \sum') = \sum_j [e^2/r_{oj}^2] F_{l(m)}$ equation (3) was used to find $F_{l(m)}$: then by equation (1), the splitting was calculated. The results are given in Table 3. When $\sum_j I_{oj}$ is negative, the *a* component should appear at lower energies than the *b*, and *vice versa*.

To calculate the actual value of the splitting it is necessary to evaluate M from experiment. When the band system marks a strongly allowed transition the total integrated intensity of the whole system may be used, the numerical value being derived from the solution spectrum. This approximation is reasonable when there is a relative absence of vibrational structure. However, as has been shown,[7] the presence of vibrational structure

TABLE 1. *Same* (001) *plane: interactions between non-equivalent molecules.*

Pair: o and	Durene		Ovalene		Metal-free phthalocyanine	
	l	*m*	*l*	*m*	*l*	*m*
C, D, E, or F	−352	414	−133	85	70	−124
G, L, S, or M	67	103	−24	56	48	−22
U, T, V, or W	36	31	10	30	26	10
I, J, P, or Q	−28	21	−6	3	3	−6
H, K, N, or R	−13	15	−5	3	3	−5
X_1, X_2, X_3, or X_4	2	10	−3	3	2	−3
Y_1, Y_2, Y_3, or Y_4	−7	5	−1	1	1	−1
Σ	−295	599	−163	182	151	−150

TABLE 2. *Adjacent* (001) *plane: interactions between inequivalent molecules: and total interaction* (cm.$^{-1}$ Å^{-2}).

Molecule paired with o	Durene		Ovalene		Metal-free phthalocyanine	
	l	*m*	*l*	*m*	*l*	*m*
C′ or D′	−80	24	−41	9	(11) *	(−4) *
G′ or L′	− 3	24	−20	9	*	*
U′ or V′	12	14	− 8	9	*	*
F′ or G′	43	−338	−12	−86	−63	−17
S′ or M′	69	−8	20	−35	−31	2
T′ or W′	34	13	20	−5	−7	11
Q′ or N′	−31	−7	*	*	*	*
Σ'	46	−278	−50	−99	−101	−4
$4\Sigma'$	184	−1112	−200	−396	−404	−16
4Σ	−1180	2394	−652	726	607	−601
$4\Sigma + 4\Sigma'$	−996	1282	−852	330	203	−617

* Molecule separation greater than 20 Å.

TABLE 3. *Splittings for l and m polarized molecular transitions* (cm.$^{-1}$).

	ν (cm.$^{-1}$)	Region considered (cm.$^{-1}$)	f	M^2 (Å)^2	$E_\alpha - E_\beta$ *l* [cm.$^{-1}$]	*m* [cm.$^{-1}$]
Durene	36,000	35,000—41,000	0·008	0·022	−40	60
	49,300	45,000—46,000	*ca.* 0·13	0·27	−540	700
Ovalene	21,900	21,700—22,700	0·08	0·35	−600 *	230 *
	23,100	22,700—23,800	0·055	0·22	−380 *	150 *
	24,600	23,800—25,600	0·05	0·20	−340 *	130 *
	21,900	21,300—26,300	0·22	0·8	−1400	500
	28,700	26,300—33,400	1·2	0·34	−600	220
Metal-free phthalocyanine	14,290	14,100—14,400	0·1	0·7	280 *	−860 *
	15,060	14,900—15,200	0·1	0·7	280 *	−860 *

* Denotes vibrational bands considered separately.

results in the various bands' each being split. To apply the previous method would give a result which would represent the sum of the splittings of the individual bands.

Allowance for vibrational structure demands that if I_{oj} is defined in terms of purely electronic functions ϕ, the splitting given by equation (1) should be multiplied by ξ^2 where $\xi = \int \sigma(o) \cdot \sigma'(n)\, d\nu_{vib}$ in which σ, σ' refer to vibrational functions of the ground and excited electronic states and the quantum state of the vibration is given in parentheses.

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The quantities ξ^2 are evaluated from the solution spectrum. This approach has been used in those cases which are denoted in Table 3 by an asterisk. There will be an interaction between different vibrational quantum states of the one electronic level as well as between different electronic levels. These refinements have been discussed by Craig [7] but may be neglected when the splitting is small compared with the vibrational spacing.

The application of the results is chiefly to predict features of the crystal spectra from the known molecular (solution) spectra. When the crystal spectra become available it should be possible to use Table 3 to determine the polarization of the molecular transitions. This may be done on two bases: (*a*) The sign of the splitting varies with the polarization of the molecular transition. A determination of whether the *a* or the *b* component lies at longer wavelengths is in the case of non-degenerate levels therefore sufficient to find the polarization. (*b*) The magnitude of the splitting gives an indication of how far apart in the spectrum related bands may be found. This is not so necessary for weak bands where the relation should be obvious, but as is seen in Table 3 strong bands may have components separated by hundreds of Ångström units and their relation is not likely to be obvious. (This was the case with anthracene and interpretation of the crystal spectrum was hindered for a long time as a result.)

Durene and ovalene are considered to have a molecular symmetry described by the group D_{2h}. In these cases the use of the integrals to calculate the splitting is not complicated by the presence of degenerate levels.

In durene the first two electronic transitions become electronically allowed if the corresponding transitions in benzene are $B_{2u} \leftarrow A_{1g}$ and $B_{1u} \leftarrow A_{1g}$. The expected polarizations are *l* and *m* respectively. In the crystal therefore the two transitions should be split differently, by -40 and $+700$ cm.$^{-1}$ respectively. However, if the 2000 Å benzene transition is $E_{2g} \leftarrow A_{1g}$, made allowed by vibrations,[12] then four components should appear in the crystal, involving both molecular polarizations. The presence of vibrational structure reduces the expected splitting. At 90° K seven main peaks appear [13] in the 2800 Å transition. The splitting in each of these is, therefore, expected to be only a few tenths of an Ångström unit. Certainly no splitting appreciably larger than this appeared at 90° K but the actual value has not yet been measured.

In ovalene the *l* direction passes through the centres of several C–C bonds, the *m* direction through four C atoms. The splitting of a vibrational level is expected to be of the order of 100 cm.$^{-1}$ whatever the polarization of the molecular transition. From the polarization of the longer-wavelength component it should be possible to determine the transition polarization.

The spectra of metal phthalocyanines in general resemble the spectrum of metal-free phthalocyanine, which in solution shows a series of absorption maxima. It has been suggested [14] that two electronic transitions are present with origins at 14,290 and 15,060 cm.$^{-1}$. It is not clear that this must be the case and that a 770 cm.$^{-1}$ vibrational interval is not responsible. A further possibility arises from a consideration of the molecular symmetry. At least in the crystal the molecular symmetry either, most strictly, is described by C_{2h} or, if the two hydrogen atoms are ignored, by D_{2h}. The departure from D_{4h} symmetry is not great, but is quite definite. The significance of the departure from D_{4h} is hard to determine quantitatively. It is roughly estimated in cm.$^{-1}$ from the separation of the four central nitrogen atoms as of the order of a molecular vibration. It may be suggested tentatively that the 14,290 and 15,060 cm.$^{-1}$ bands are components of a transition which in D_{4h} would be terminated by a degenerate level. The question of the splitting of a degenerate level in phthalocyanine and in coronene will be discussed in a later paper. The similar problem in the case of benzene has been treated by Craig and Walsh.[15] The

[12] Craig, *Proc. Roy. Soc.*, 1950, *A*, **200**, 401; Dunn and Ingold, *Nature*, 1955, **176**, 65.
[13] Lyons and Walsh, unpublished work.
[14] Anderson, Bradbrook, Cook, and Linstead, *J.*, 1938, 1152.
[15] Craig and Walsh, *J.*, in the press.

splittings quoted in Table 3 will be relevant to observation only if the effective molecular symmetry is D_{2h} and not D_{4h}. The *l* polarized splitting is rather less than the 14,290—15,060 interval, but the *m* polarized splitting is comparable in magnitude with this interval and is therefore but a first approximation. Observation of the spectrum should be able easily to differentiate between *l* and *m* polarization.

The author is grateful for the hospitality of Professor William Moffitt and the Department of Chemistry, Harvard University, and thanks the U.S. Educational Foundation for a travel grant. Professor D. P. Craig and Mr. J. R. Walsh are thanked for valuable comments on the manuscript.

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272. *Tricalcium Silicate Hydrate.*

By E. R. BUCKLE, J. A. GARD, and H. F. W. TAYLOR.

The composition is shown to be $3CaO,SiO_2,1\frac{1}{2}H_2O$, and the ionic constitution possibly $Ca_6(Si_2O_7)(OH)_6$. Hydrothermal formation from anhydrous tricalcium silicate at 180—500° is confirmed. Optical and electron-microstope studies show that the compound crystallises in long, thin needles or fibres which often have foil-like (possibly tubular) extensions at the ends. From single-crystal electron-diffraction and powder *X*-ray data the unit cell is shown to be geometrically hexagonal or trigonal with $a = 10{\cdot}00$, $c = 7{\cdot}48$ Å, with strong pseudo-halving of *c*, and atomic contents $Ca_{12}Si_4O_{26}H_{12}$. The *X*-ray density is 2·61 g. cm.$^{-3}$. Dehydration occurs within the range 420—550°; the products at 700° are γ-Ca_2SiO_4 and lime.

TRICALCIUM SILICATE HYDRATE * ($3CaO,SiO_2,xH_2O$) has usually been obtained by hydrothermal treatment of anhydrous tricalcium silicate,[1-4] although it can also be made hydrothermally from mixtures of less basic hydrated calcium silicates with calcium hydroxide.[4] The water content (x) has usually been taken as 2, but values ranging from 1·3 to 2·0 have been reported. Optical data for crystalline aggregates are well established; a typical description [4] is of broad, fibrous crystals with parallel extinction, positive elongation, low birefringence, and indices α 1·590, γ 1·602, both $\pm$0·003. *X*-Ray data [3,5,6] are not in complete agreement, which suggests that some or all of the preparations may have been impure. The specific gravity has been reported [2] as 2·56 for a preparation with $x = 1{\cdot}6$. Dehydration is reported to occur between 500° and 900°, the final products being CaO and β- or γ-Ca_2SiO_4.[3,4]

Work in progress by us confirms earlier suggestions [3] that tricalcium silicate hydrate may occur in steam-cured Portland cement pastes, and a fuller study of its properties seemed desirable. The main aims of the present work were: (i) to study the morphology; (ii) to establish the unit-cell and obtain reliable *X*-ray powder data; (iii) to determine the water content and more exact conditions of thermal dehydration with a view to developing a thermogravimetric technique for its estimation. Further results were obtained concerning the conditions of formation and are now partly reported; experiments relating mainly to the setting of tricalcium silicate pastes will be fully described elsewhere.

* The terms " hydrate " and " hydrated calcium silicate " as used in this paper, do not necessarily imply presence of water molecules. The broad usages are well established in the literature on calcium silicates.

[1] Bessey, Report of the Building Research Board, 1935 (London, 1936; H.M.S.O.), **36**.
[2] *Idem*, Proc. Symp. Chem. Cements, Stockholm, 1938, 178.
[3] Keevil and Thorvaldson, *Canad. J. Res.*, 1936, *B*, **14**, 20.
[4] Flint, McMurdie, and Wells, *Bur. Stand. J. Res.*, 1938, **21**, 617.
[5] McMurdie and Flint, *ibid.*, 1943, **31**, 225.
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Experimental

Preparation.—Tricalcium silicate hydrate was prepared, approximately as described by Flint *et al.*,[4] by suspending tricalcium silicate (particle size <20 μ) in water and autoclaving it at various temperatures above 200°. A poorly-crystalline synthetic tobermorite, mixed with calcium oxide to give Ca : Si = 3 : 1, was also successfully used as starting material. Suspensions were contained in stainless-steel bombs of about 7 ml. capacity, closed with screw stoppers and copper gaskets. The bombs were heated in a thermostatted electric oven for temperatures below 300°, or for higher temperatures in an electric furnace. The products were washed out of the bombs with acetone and recovered by filtration. After a final wash with light petroleum they were dried in a vacuum desiccator and stored in tubes with waxed stoppers.

Details, with results of *X*-ray and optical examination of the products, are given in Table 1. In all cases, products are listed in apparent decreasing order of abundance. In no preparation was tricalcium silicate hydrate the sole product. The most usual impurity was a phase, or

Table 1. *Preparations, with results of X-ray and optical examination.*

Specimen No.	Starting material(s) *	Temp.	Time of autoclaving	Phases detected in product: * by *X*-rays	optically
SD93	C_3S	180°	6 hrs.	TSH, CH	TSH, T, CH, $C\bar{C}$
A100	C_3S	250	9 days	α, CH, TSH	α, TSH, $C\bar{C}$
A124	C_3S	275	7 days	α, CH, TSH	TSH, α, $C\bar{C}$
A66	C_3S	375	6 days	TSH, γ	TSH, γ, $C\bar{C}$
A69	C_3S	375	8 days	TSH, γ	TSH, γ, $C\bar{C}$
A75	C_3S	375	17 days	TSH, γ	TSH, γ, $C\bar{C}$
A77	C_3S	375	32 days	TSH, γ	TSH, γ, $C\bar{C}$
A73	T + CaO	375	24 days	TSH, γ	TSH, γ, CH, $C\bar{C}$
A79	C_3S	430	62 hrs.	TSH, γ	TSH, γ, $C\bar{C}$
A78	C_3S	500	5 days	γ, TSH	CH, α, γ, $C\bar{C}$

* Abbreviations: C_3S, tricalcium silicate; TSH, tricalcium silicate hydrate: CH, calcium hydroxide; $C\bar{C}$, calcium carbonate (calcite); T, tobermorite; α, dicalcium silicate α-hydrate [dicalcium silicate hydrate (A)]; γ, gamma-hydrate(s) (see text).

possibly a mixture of closely similar phases, resembling dicalcium silicate γ-hydrate [dicalcium silicate hydrate (*C*)]. Throughout this paper this will be termed "gamma-hydrate(s)." Table 1 also includes data for a preparation (SD93), kindly supplied by Mr. G. E. Bessey, made by autoclaving a tricalcium silicate–water paste.

Optical Examination.—All products contained clusters of extremely thin fibres or needles, often 100 μ long, interspersed with prismatic material. With most preparations the fibres were visible only when immersed in a liquid of very different refractive index. Plate 1 shows material from A79 immersed in liquid paraffin ($n = 1{\cdot}48$). Fibres from SD93 were of sufficient size for some optical properties to be determined. The results [|| extinction, + elongation, α(or ω) 1·593, γ(or ε) 1·597, both ±0·003] agreed with those of earlier workers.[1-4]

Electron Microscopy and Diffraction.—Specimens, prepared by crushing lightly in water and allowing drops of the suspensions to evaporate on Formvar-coated specimen grids, were examined with a Metropolitan-Vickers EM3 electron microscope. A typical electron micrograph (Plate 2) of material from A77 shows the principal constituent to be long, narrow, lamellar fibres, 500—2500 Å wide, and up to 100 μ long. The fibres terminate in extremely thin foils, which appear to be either trough-shaped or tubular in section. Prismatic crystals, which could have been calcite or gamma-hydrate(s), are also visible.

Electron-diffraction patterns from individual fibres showed them to be single crystals. Interpretation of such patterns and a procedure for estimation of the "third row" lattice spacing from the radii of Laue zones have been described.[7] Plate 3(*a*) shows a typical diffraction pattern; a few were also recorded of the type shown in Plate 3(*b*), suggesting a different orientation around the fibre axis. The mean spacing in the fibre direction, which will be called *c*, was 7·5 ± 0·1 Å. As reflections on all the patterns fell on orthogonal nets, *c* coincides with c^*.

[7] Gard, *Brit. J. Appl. Phys.*, 1956, **7**, 361; *J. Sci. Instr.*, 1956, **33**, 307.

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PLATE 1. *Photomicrograph of fibres of tricalcium silicate hydrate, immersed in liquid paraffin.* (The ruled line represents 10 μ.)

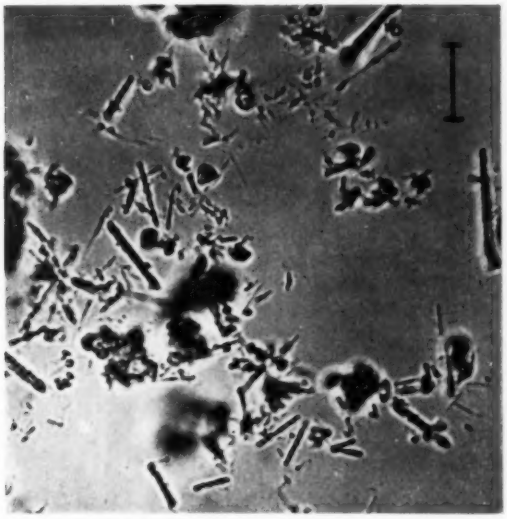

PLATE 2. *Electron micrograph of tricalcium silicate hydrate; stereo-pair showing acicular crystals with foil-like projections.* (The ruled line represents 1 μ.)

[*To face p.* 1352.

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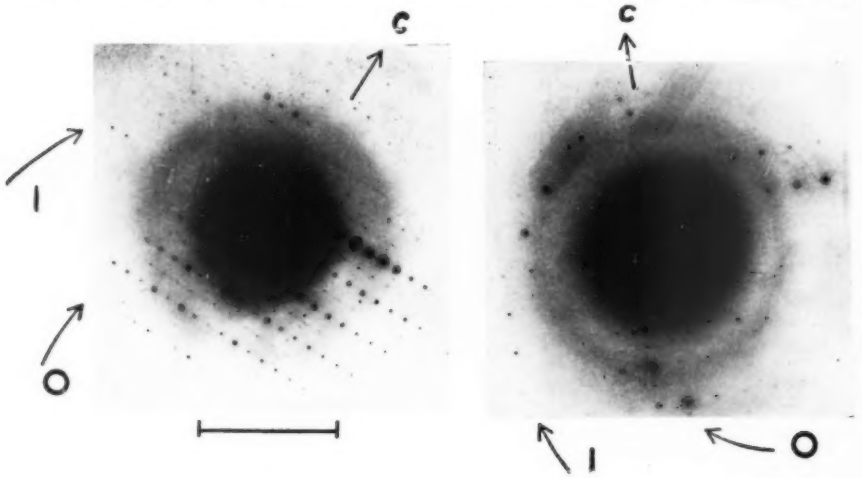
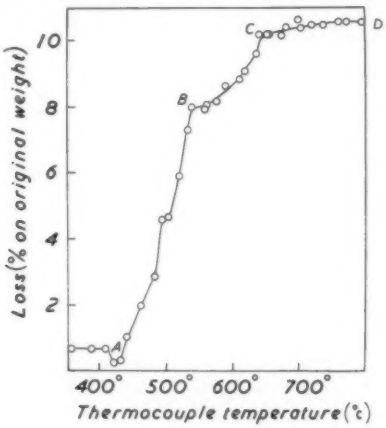
PLATE 3. *Electron-diffraction patterns from single crystals of tricalcium silicate hydrate lying on* (*a*) $(11\bar{2}0)$, *and* (*b*) $(10\bar{1}0)$. *Arrows show the fibre direction c. In both patterns, odd layers normal to c are weak and slightly streaky, and the rows of spots parallel to c in the first-order Laue zone* (marked 1) *lie halfway between the corresponding rows in the zero-order zone* (marked 0). (The rule line represents 1 $Å^{-1}$.)



(*a*) (*b*)

FIGURE. *Dehydration isobar for specimen* A79, *obtained at* $p(H_2O) = 6$ *mm.*: *AB*, dehydration of tricalcium silicate hydrate; *BC*, decomposition of calcite; *CD*, dehydration of gamma-hydrates.



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Relative positions of spots on adjacent Laue zones indicated a *C*-centred reciprocal lattice. From the type of pattern shown in Plate 3(*a*) the spacing normal to *c* in the plane of the supporting film was found to be 17·2 Å, and the spacing parallel to the beam, estimated from the radii of Laue zones, was about 10·5 Å. Corresponding values for the pattern shown in Plate 3(*b*) were 10·0 and about 16·5 Å, respectively. These results confirm that the patterns correspond to different orientations around *c*, and indicate a *C*-centred orthorhombic unit cell with $a = 17{\cdot}2$, $b = 10{\cdot}0$, $c = 7{\cdot}5$ Å. This is, at least geometrically, equivalent to a hexagonal or trigonal unit cell with $a = 10{\cdot}0$, $c = 7{\cdot}5$ Å. Since no systematic absences were observed, the unit cell is not rhombohedral. The frequency with which fibres gave patterns of the type shown in Plate 3(*a*) suggests that the principal cleavage is $(11\bar{2}0)$. Reflections with *l* odd were systematically weak, and were slightly streaked in the plane normal to *c**. In all the patterns, 0004 was stronger than other *hki*4 reflections.

An unsuccessful attempt was made to identify the thin foils projecting from the ends of the crystals. Long exposures were used, with an intermediate aperture that selected an area 0·5 μ in diameter. To ensure accurate focusing of any diffraction pattern, a device was fitted that permitted a reproducible advance to the objective lens current from the setting at which the normal image was in true focus. In spite of this, no diffraction patterns could be obtained.

X-Ray Powder Investigation.—*X*-Ray powder data were obtained by using a Philips 11·46 cm. diameter camera with filtered copper radiation. As indicated in Table 1, all specimens gave patterns containing lines due to other phases. The patterns were compared with each other and with those of all likely impurities, and also with those of the heated specimens described later. The lines of the tricalcium silicate hydrate were thus distinguished and are listed in Table 2. Relative intensities were estimated visually. The unit-cell parameters derived

TABLE 2. *X-Ray powder data for tricalcium silicate hydrate, indexed on a hexagonal unit cell with* $a = 10{\cdot}00$, $c = 7{\cdot}48$ Å.

Spacings (Å), obs.*	Indices	Spacings (Å), calc.	Spacings (Å), obs.*	Indices	Spacings (Å), calc.	Spacings (Å), obs.*	Indices	Spacings (Å), calc.
8·6 vs	10·0	8·66	2·44 mw	21·2	2·46		10·4	1·827
5·01 ms	11·0	5·00		31·0	2·40	1·753 ms	32·2	1·756
4·24 w	20·0	4·33	2·28 mw	30·2	2·28		11·4	1·752
3·78 m	0002	3·74	2·16 mw	40·0	2·16		50·0	1·732
	10·2	3·43	**2·08 s**	22·2	2·08		20·4	1·717
3·28 s	21·0	3·27		31·2	2·02	1·682 ms	41·2	1·686
3·03 s	11·2	3·00	1·986 m	32·0	1·988	1·666 vw	33·0	1·667
2·89 s	30·0	2·89	1·897 m	41·0	1·890	1·636 vvw	42·0	1·640
2·82 m	20·2	2·83	**1·870 s**	40·2	1·874			
2·49 w	22·2	2·50		0004	1·870			

* Also: 1·557 vvw, 1·497 w, 1·438 w, 1·357 w, 1·247 w, 1·229 w, 1·208 w, 1·176 mw, 1·144 mw, 1·02 m, 0·981 mw.

from the electron-diffraction data were refined by correlation with the *X*-ray powder pattern. This could be indexed completely on a hexagonal or trigonal unit cell with $a = 10{\cdot}00$, $c = 7{\cdot}48$ Å, both $\pm 0{\cdot}03$ Å. The exact value of *c* followed from the assumption that the strong reflection at 1·870 Å is 0004. Reflections having odd values of *l* were ignored as they were weak in the electron-diffraction patterns, although they may contribute to the intensities of some lines in the *X*-ray pattern. Table 2 gives observed and calculated values for all spacings greater than 1·63 Å, and having *l* even; below this the choice of indices was not unique. Since reflections 10·2, 31·2, 10·4, 50·0, and 20·4 are present in the electron-diffraction pattern, though absent from the *X*-ray powder pattern, there are no systematic absences. Agreement between observed and calculated *d*-spacings is good, and supports the view that all the spacings listed in Table 2 are those of tricalcium silicate hydrate.

Densities.—Samples were compressed into pellets by mean of a screw-press and immersed in bromoform–benzene. The pellet was freed from trapped air by outgassing under reduced pressure, and the density of the liquid progressively raised by pumping off benzene. When the pellet could be suspended without movement, the density of the liquid was measured with a pycnometer. Densities obtained, probably reliable to $\pm 0{\cdot}01$ g. cm.$^{-3}$, were: SD93, 2·49; A79, 2·64; A77, 2·68; A66, 2·69; A75, 2·72 g. cm.$^{-3}$.

Dehydration Isobars.—These were determined by using a helical silica spring balance enclosed in a vertical column. The lower part of this column, which contained the specimen in

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a platinum boat, was of silica and passed through an electric tube-furnace. Temperatures were measured with a thermocouple within the silica tube, and as the specimen lost weight the upper end of the silica spring was lowered so that the platinum boat was always just clear of the thermocouple. A continuous, downward flow of carbon dioxide-free air at 6 mm. partial pressure of water vapour was maintained through the column, the lower end of which was fitted with a series of guard tubes to exclude carbon dioxide. Where practicable, spring extensions were recorded at 4-hourly intervals and the temperature was raised by 5—10° when the loss between successive weighings fell to within experimental error. A complete run took about 14 days. Dehydration was usually complete by about 750°.

Isobars were obtained for specimens SD93, A79, A77, A66, and A75. A typical one, for A79, is given in the Figure. The impurities in this specimen were calcite and gamma-hydrate(s) (Table 1). Separate experiments showed that, under the conditions used, calcite decomposed within the range 550—650° and gamma-hydrate(s) at 650—750°. The portion *AB* of the curve in the Figure at 420—550° therefore corresponds to dehydration of the tricalcium silicate hydrate, while *BC* and *CD* correspond to decomposition of the calcite and the gamma-hydrate(s) respectively. The small drop in the curve near *A* was possibly caused by dehydration of a trace of calcium hydroxide and subsequent absorption of carbon dioxide which, despite all precautions, entered the apparatus.

X-*Ray Examination of Heated Material.*—Specimens were heated to constant weight at various temperatures under the conditions used for determination of dehydration isobars, and subsequent *X*-ray powder photographs gave the results in Table 3. " A " denotes an unidentified phase or mixture of phases giving the following pattern (spacings in Å): 4·9 w,

Specimen	Temp.	Phases detected	Specimen	Temp.	Phases detected
A75	Unheated	TSH, γ	SD93	550°	" A "
,,	450°	TSH, γ	,,	600	" A "
,,	600	γ	,,	700	γ-Ca_2SiO_4, CaO
SD93	Unheated	TSH, CH	A66	Unheated	TSH, CH
,,	500°	" A "	,,	960°	β-Ca_2SiO_4, γ-Ca_2SiO_4, CaO
,,	525	" A "			

4·3 w, 3·77 m, 3·32 vw, 3·01 s, 2·87 w, 2·73 vs, 2·66 w, 2·60 w, 2·51 mw, 2·46 vw, 2·39 vw, 2·27 vw, 2·18 mw, 2·03 w, 1·90 s, 1·80 mw, 1·75 w, 1·69 mw, 1·66 w, 1·54 w, 1·50 vw, 1·46 w. Most of the lines were broad. With the specimen of A75 heated at 600°, γ-Ca_2SiO_4, or " A ", or both, could also have been present, as the strong lines of both coincide with ones of gamma-hydrate(s). With the specimen of SD93 heated at 700°, the 2·18 Å line of γ-Ca_2SiO_4 was abnormally strong.

Discussion

Conditions of Formation, and Characterisation of Tricalcium Silicate Hydrate as a Distinct Compound.—The hydrothermal synthesis of tricalcium silicate hydrate reported by earlier workers has been confirmed, and the difficulty of obtaining a pure specimen demonstrated. Products made below about 300° contained also calcium hydroxide together with tobermorite or dicalcium silicate α-hydrate, while at higher temperatures gamma-hydrate(s) were the main impurity. The proportion of these relative to tricalcium silicate hydrate appears to increase sharply with temperature above about 430°. Earlier workers seem to have had the same difficulty in trying to make pure material. Keevil and Thorvaldson's *X*-ray data [3] closely resemble those of specimen A66, which contained gamma-hydrate(s). McMurdie and Flint's data [5] for a product made [4] at 250° indicate that it was substantially free from gamma-hydrate(s). Experiment A100 (Table 1) was an attempt to repeat this preparation, but it gave a product contaminated mainly by dicalcium silicate α-hydrate and calcium hydroxide.

The status of tricalcium silicate hydrate as a distinct compound is confirmed. Kalousek, Logiudice, and Dodson [8] noted similarities between the *X*-ray powder patterns of tricalcium silicate hydrate, hillebrandite ($2CaO,SiO_2,H_2O$), and foshagite [9] ($4CaO,3SiO_2,H_2O$), and suggested that the three substances might belong to a structurally

[8] Kalousek, Logiudice, and Dodson, *J. Amer. Ceramic Soc.*, 1954, **37**, 7.
[9] Gard and Taylor, *Amer. Min.*, 1958, **43**, 3.

related series of variable composition. Comparison of the unit cells of tricalcium silicate hydrate, foshagite,[9] and hillebrandite [10] does not support this view.

Water Content and Density.—Attempts to determine the water content directly from the dehydration isobar gave inconclusive results because of uncertainties about the composition and proportions of the admixed tobermorite or gamma-hydrate(s). The water content was therefore estimated indirectly from the unit-cell volume and the density (D). The latter must lie between that of SD93 (2·49) and that of A79 (2·64), because the principal impurities in SD93 (tobermorite and calcium hydroxide) have densities below 2·49 while the gamma-hydrate(s) in A79 have densities near 2·83. Taken in conjunction with the unit-cell volume this indicates the unit-cell content $4[3CaO,SiO_2,xH_2O]$ where x lies between 0·8 and 1·7. Closer estimates of D and x were obtained as follows. The density can be calculated for any postulated water content either from the X-ray data ($D = 1{\cdot}66M/V$) or from the mean refractive index by using the Lorentz–Lorenz relation. The latter method gives results usually reliable to within $\pm 2\%$ for calcium silicates if the empirical atomic refractions Ca = 3·25, O = 3·65, and Si = H = 0 are used.[11] The two methods give results that vary in opposite senses with x. The values of density and water content consistent with both methods are $D = 2{\cdot}60$, $x = 1{\cdot}42$. In view of the uncertainties involved in the calculation from refractive index, the formula $3CaO,SiO_2,1\frac{1}{2}H_2O$ is suggested. The corresponding X-ray density is 2·61 g. cm.$^{-3}$.

The previously accepted formula $3CaO,SiO_2,2H_2O$ seems to have been based mainly on a water content of 13·56% found by Flint *et al.*[4] for a specimen made at 275°. However, the specimen made at 250°, for which the X-ray data were afterwards reported, contained only 11·53% of water, giving $x = 1{\cdot}63$. They also report a loss of 10·1% over the range 215—700° for an unspecified preparation; this indicates $x = 1{\cdot}42$. Bessey [1,2] found about 1·6 mol. of water firmly bound and a density of 2·56, which agrees substantially with the present result.

Dehydration.—The isobar (Figure) and X-ray evidence show that water is lost at 420—550°. From the loss over this range the proportion of tricalcium silicate hydrate in A79 can be estimated as about 75%. Dehydration seems to occur in two approximately equal stages; the intermediate arrest, although slight, appears genuine, as it was found with all the specimens studied; its significance is not known. The X-ray pattern of " A," given by specimens heated at 500—600°, resembles that of γ-Ca_2SiO_4 [6] but shows significant differences. As lime was not detected below 700°, it may have been formed initially in a poorly-crystallised condition; it is also possible that some of the expelled lime could have been incorporated in the γ-Ca_2SiO_4, thereby affecting its powder pattern. Even with the specimen heated at 700°, the γ-Ca_2SiO_4 pattern was slightly anomalous. It thus appears that dehydration gives γ-Ca_2SiO_4 and lime, but crystallisation of these develops gradually with rise of temperature.

Constitution.—The fact that tricalcium silicate hydrate can be formed at temperatures as high as 500°, together with the relatively high temperature of dehydration, suggests that the water may be present as hydroxyl not attached to silicon, though this cannot be considered certain. This hypothesis supports the ionic formula $Ca_6(Si_2O_7)(OH)_6$ proposed by Bessey.[1] The weakness of reflections with l odd suggests, by analogy with other calcium silicates, that the calcium–oxygen pattern may repeat at intervals of $c/2$, and the streaking of these reflections similarly suggests disorder in the positions of the Si_2O_7 groups.

We thank the Johns-Manville Corporation (Manville, N.J., U.S.A.) for generous financial support and permission to publish the work, Mr. G. E. Bessey (Chalk, Lime and Allied Industries Research Association, Welwyn) for specimen SD93, and Dr. R. W. Nurse (Building Research Station, Watford) for the specimen of tricalcium silicate.

UNIVERSITY OF ABERDEEN. [*Received, August 23rd*, 1957.]

[10] Heller, *Min. Mag.*, 1953, **30**, 150.
[11] Howison and Taylor, *Mag. Concrete Res.*, 1957, **9**, 13.

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273. *The Reactivity of Esters of Quinquevalent Phosphorus towards Anions.*

By R. F. Hudson and D. C. Harper.

The rate of reaction of trimethyl phosphate, dimethyl ethylphosphonate, and dibenzyl methylphosphonate with a series of anions follows the redox potentials of the ions fairly closely. This is considered to be characteristic of a bimolecular displacement reaction at the saturated carbon atom. The high reactivity of the hydroxide ion is attributed to alternative reaction at the phosphorus atom.

Previously,[1] the effect of substitution on the rate of alkaline hydrolysis of phosphonate esters was discussed in terms of a displacement reaction at the phosphorus atom. Although the evidence in favour of this reaction is highly suggestive, the possibility of alternative substitution at the saturated carbon atom of the ester group cannot be definitely excluded in view of the high yields of ethers obtained on trans-esterification.[1b] The possibility of differentiating between these alternative reactions by kinetic measurements has been considered in the following way. It is well known that certain anions, in particular highly polarisable ions, *e.g.*, I^- and $S_2O_3^{2-}$, are very reactive towards the saturated carbon atom. Rate measurements indicate a common order of reactivity [2] in the bimolecular displacement reactions of alkyl halides, sulphonates, epoxides, and β-lactones. Moreover, the reactivities of a series of ions towards any two of these alkylating agents can be represented fairly closely [2] by the relation

$$\log k_2 = \text{const.} \times \log k_2^1 + \text{const.}$$

where k_2 and k_2^1 are rate constants for the reactions of a particular ion with these two reactants. This linear relation suggests that the reactivity of a particular ion can be represented by a parameter characteristic of the ion but independent of the substrate. When, however, the nature of the transition state changes considerably, *e.g.*, to an ionisation process, the common order of anion reactivity no longer prevails.

As a result of detailed measurements of the rates of substitution of several chalcogens with anionic reagents, Foss [3] noted a close relation between the reactivity and the redox potential of the ion. A similar relation is found to hold approximately for the bimolecular substitution reactions of the alkylating agents so far examined.[4]

If attention is confined to S_N2 displacements only, the rate constant k_2 can be related to the redox potential E_r as follows,

$$\log k_2 = \alpha E_r + \log k^\circ_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where α is a constant characteristic of the substrate, and k°_2 is the rate constant of a reference reaction, *e.g.*, solvolysis.

The proportionality between the free energy of the substitution reaction and the oxidation–reduction potential shows that the energy changes in the two processes are determined by similar factors:

$$(a)\ N^- + R{-}X \rightleftharpoons N^{\delta-} \cdots R \cdots X^{\delta-}$$

$$(b)\ N^- \rightleftharpoons \tfrac{1}{2}N_2 + e$$

In both processes the energy of electron transfer from the ion N^-, and the resultant change in solvation energy are more significant than the energy of the bond formed. This is also

[1] (*a*) Hudson and Keay, *J.*, 1956, 2463; (*b*) Toy, *J. Amer. Chem. Soc.*, 1944, **66**, 499; Rueggeberg and Chernak, *ibid.*, 1948, **70**, 1802.
[2] Scott and Swain, *ibid.*, 1953, **75**, 141.
[3] Foss, *Acta Chem. Scand.*, 1947, **1**, 8, 307; 1949, **3**, 1385.
[4] Edwards, *J. Amer. Chem. Soc.*, 1954, **76**, 1540.

shown by semi-empirical calculations of the activation energies of substitution reactions.[5] For the present purpose a detailed interpretation of equation (1) is not required.

A similar energy balance is not to be expected in reactions with widely varying transition states, and Edwards [4] has demonstrated the necessity of a four-parameter equation in relating the rate to the properties of the ion. Thus he found that the rate of a wide range of reactions could be represented as a linear function of the oxidation–reduction potential and the pK_a of the conjugate acid of the nucleophil. An examination of the limited data on the rate of substitution at the phosphoryl centre shows that anions which are the most reactive towards the saturated carbon atom are amongst the least reactive nucleophils towards phosphorochloridates, as shown by the rate sequence given by Dostrovsky and Halmann: [6]

$$OH^- > F^- > OMe^- > OPh^- > EtOH > PhS^-, AcO^-$$

The reactivity of a particular ion is highly dependent on the basicity (towards protons) relative to that of the displaced group.[7] Thus, although fluoride and phenoxide ions readily react with phosphorochloridates, they are unreactive towards esters in protolytic solvents. In general, it may be assumed that an ion does not displace a more basic group from a phosphoryl group at a measurable rate in a solvolytic medium, and consequently the number of anions which can displace alkoxy-groups from esters is very limited. For example, the hydroperoxide ion is highly reactive towards acyl halides, anhydrides, and aromatic esters but is inert towards aliphatic esters.[7]

These considerations suggest strongly that only the most basic anions can remove the alkoxy-groups from phosphorus esters at an appreciable rate by attack at the phosphorus atom. Anions of strong acids will react preferentially at the carbon atom as shown, for example, by the ready reaction of lithium chloride with benzyl phosphates.[8]

TABLE 1.

Nucleophilic reagent	k_1 (min.$^{-1}$)	$\log\frac{k_2}{k_{H_2O}}$	k_1 (min.$^{-1}$)	$\log\frac{k_2}{k_{H_2O}}$	k_1 (min.$^{-1}$)	$\log\frac{k_2}{k_{H_2O}}$
	$PO(OMe)_3$ *		$Et{\cdot}PO(OMe_2)_2$ *		$Me{\cdot}PO(O{\cdot}CH_2Ph)_2$ †	
Water	$2{\cdot}02 \times 10^{-2}$	0	$1{\cdot}5 \times 10^{-2}$	0	$6{\cdot}4 \times 10^{-2}$	0
Chloride	$0{\cdot}49 \times 10^{-2}$	1·83	$0{\cdot}3 \times 10^{-2}$	1·74	$8{\cdot}3 \times 10^{-2}$	2·46
Bromide	$2{\cdot}40 \times 10^{-2}$	2·52	$1{\cdot}8 \times 10^{-2}$	2·52	$11{\cdot}9 \times 10^{-2}$	2·61
Thiocyanate	$8{\cdot}71 \times 10^{-2}$	3·07	$3{\cdot}04 \times 10^{-2}$	3·75	$72{\cdot}4 \times 10^{-2}$	3·38
Iodide	$4{\cdot}65 \times 10^{-2}$	2·81	$7{\cdot}02 \times 10^{-2}$	3·10	$4{\cdot}7 \times 10^{-2}$	3·41
Thiosulphate	4·51	4·79	0·21	4·58	3·47	4·07
Hydroxide	1·67	6·09	4·70	7·40	59·0	5·31
‡ Hydroxide (estimated)	—	2·75	—	2·60	—	2·60

* With 0·2N-anion in water at 80°. † With 0·2N-anion in 25% acetone + 75% water at 100°.
‡ Estimated from equation (1).
k_1 is the first-order constant for the reaction with a particular anion of concentration [X], see equation (2): $k_2 = k_1/[X]$.

It is proposed, therefore, to relate the rate constants for the reaction of a series of anions with a particular ester to the redox potential E_r, according to equation (1). Abnormally high reactivities of highly basic ions may then be attributed to the reaction at the phosphoryl group. This principle can be illustrated by the well-known alkylation of β-lactones. Isotope analysis shows that the neutral hydrolysis proceeds with alkyl–oxygen fission,[9] and the rate of reaction with a series of anions [10] is given closely by equation (1). The hydroxide ion is, however, *ca.* 10^3 times more reactive than predicted by this equation, indicating preferential reaction at the carbonyl group. This has been confirmed [9] by ^{18}O tracer work.

[5] Baughan and Polanyi, *Trans. Faraday Soc.*, 1941, **37**, 648.
[6] Dostrovsky and Halmann, *J.*, 1953, 502.
[7] Wiberg, *J. Amer. Chem. Soc.*, 1955, **77**, 2521.
[8] Clark and Todd, *J.*, 1950, 2030.
[9] Long and Purchase, *J. Amer. Chem. Soc.*, 1950, **72**, 3267; Olsen and Miller, *ibid.*, 1938, **60**, 2687.
[10] Bartlett and Small, *ibid.*, 1950, **72**, 4867.

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In the present investigation several esters of quinquevalent phosphorus have been found to behave in a similar manner. First, trimethyl phosphate was studied, since the positions of bond fission on acid, alkaline, and neutral hydrolysis are established in this case.[11] The data given in Table 1 show the hydroxide ion to be *ca.* 10^3 times more reactive than predicted by equation (1), and considerably more reactive than the other anions. With the exception of the hydroxide ion, the rate constant is observed to increase regularly with E_T (Table 1), suggesting strongly that the reaction proceeds at the saturated carbon atom. The abnormal reactivity of the hydroxide ion is then attributed to the preferential reaction at the phosphonyl group, which has been established by ^{18}O analysis.

Similar data are given in Table 1 for methyl ethylphosphonate and benzyl methylphosphonate. No direct investigations of the position of bond fission in the alkaline hydrolysis of phosphonate esters have been made, although various observations [1,12] point to a mechanism similar to that of phosphate esters. The greatly enhanced reactivity of the esters towards the hydroxide ion compared with the other nucleophiles (Table 1) strongly supports this conclusion. It is noted that an increase in temperature reduces the difference between the reactivity towards the hydroxide and the other ions. This is no doubt due to the low energy of activation for the reaction of the hydroxide ion at the phosphonyl group [1] [14 kcal./mole (compared with the activation energy for S_N2 reactions at the saturated carbon atom (20—23 kcal./mole)].

These investigations were extended by the preparation of methyl diethylphosphinate and measurement of its rate of alkaline hydrolysis (Table 3). The rate of reaction with most of the other ions was too small to be measured satisfactorily owing to the incursion of simultaneous side reactions. An approximate value of the rate of reaction with sodium thiosulphate was obtained, and found to be almost one half of the rate of reaction with dimethyl ethylphosphonate (Table 2). In this case also the rate of alkaline hydrolysis is *ca.* 10^4 times greater than predicted from equation (1), suggesting strongly that hydroxide ions attack the phosphorus atom preferentially.

TABLE 2. *Relative reactivity of phosphorus esters towards thiosulphate and hydroxide ions in water.**

	$PO(OMe)_3$	$Et{\cdot}PO(OMe)_2$	$Et_2PO(OMe)$
$k_{S_2O_3}$	15·7	1·1	1
k_{OH}	1	4·2	5·9
pK_a of acid	1·29	2·00	3·40

* The rate constants are divided by the number of alkoxy-groups in the ester.

The effect of progressive substitution of alkoxy-groups on the rates of alkylation and phosphonylation is shown in Table 2. Although the reactivities of the mono- and di-alkyl phosphonates are very similar, the rate of reaction of the three esters with sodium thiosulphate decreases with the pK_a of the acid released. This is in agreement with the generalisation that esters of strong acids tend to be strong alkylating agents,[13] although there is no quantitative correlation between the rate of reaction and pK_a of the acid, even in the series of closely related esters investigated here.

Substitution produces small changes in the rate of the alkaline reaction, trimethyl phosphate being significantly less reactive than the phosphonates.

EXPERIMENTAL

Materials.—Commercial trimethyl phosphate (Albright and Wilson Ltd.) was purified by fractional distillation under reduced pressure, then having b. p. 97—98°/36—38 mm. (lit., b. p. 97°/36 mm.), n_D^{18} 1·3941.

Dimethyl ethylphosphonate was prepared by refluxing ethyl iodide with 1 equiv. of trimethyl

[11] Blumenthal and Herbert, *Trans. Faraday Soc.*, 1945, **41**, 611; Barnard, Bunton, Llewellyn, Oldham, Silver, and Vernon, *Chem. and Ind.*, 1955, 761.
[12] Gerrard, Green, and Nutkins, *J.*, 1952, 4076.
[13] Anbar, Dostrovsky, Samuel, and Joffe, *ibid.*, 1954, 3604.

phosphite (Arbusov reaction), itself prepared [14] by the action of phosphorus trichloride (1 mol.) on methanol (3 mol.) and diethylaniline (3 mol.) in light petroleum (b. p. 40—60°); b. p. was 70—71°/11 mm. (lit., b. p. 70°/12 mm.).

Methyl diethylphosphinate was prepared by the action of diazomethane on diethylphosphinic acid, itself prepared by reaction between thiophosphoryl chloride and ethylmagnesium iodide, followed by oxidation of the intermediate bisdiethylphosphine disulphide. Thiophosphoryl chloride (64·5 g.) was added slowly with stirring to ethylmagnesium iodide (1·5 moles) at −10°. The mixture was stored at room temp. for 12 hr. and then decomposed in 750 ml. of 10% sulphuric acid. The ether layer was separated, and the remainder extracted twice with ether. The ether was removed, leaving a pale yellow solid which, recrystallised from ether, had m. p. 74·5° (yield 65%) (Found: C, 39·4; H, 8·26. $C_8H_{20}P_2S_2$ requires C, 39·8; H, 8·27%). Hydrogen peroxide was added slowly (76·5 ml. of 100-vol.), with stirring to this *bisdiethylphosphine disulphide* (17 g.) in acetic acid (200 ml.). The mixture was filtered, water and acetic acid were removed by the water pump, and the residual oil was distilled (11 g., 62%; b. p. 138—142°/0·7 mm.; lit., b. p. 132°/1·5 mm.) (Found: C, 38·9; H, 9·0. Calc. for $C_4H_{11}O_2P$: C, 39·3; H, 9·0%). A solution of diazomethane (5 g.) in sodium-dried ether was added slowly to this diethylphosphinic acid (10 g.) in ice-cooled ether. The ether was removed, and the residual oil distilled, yielding 7 g. (63%) of *methyl diethylphosphinate*, b. p. 84—86°/9 mm., 90—94°/15 mm. (Found: C, 44·1; H, 9·6; P, 21·7. $C_5H_{13}O_2P$ requires C, 44·2; H, 9·55; P, 22·8%).

Dibenzyl methylphosphonate was prepared as follows: methylphosphonyl dichloride (44·3 g.) in dry ether (300 ml.) was added slowly and with stirring to a mixture of freshly distilled diethylaniline (100 g.) and benzyl alcohol (72 g.) in dry ether (200 ml.) at 0°. The mixture was stored overnight, and the diethylaniline hydrochloride (103 g., 95%) filtered off. The filtrate was refluxed gently for 24 hr., the ether removed, and the oil distilled (yield 85%), having b. p. 163—164°/0·05 mm., n_D^{19} 1·5479 (Found: C, 65·0; H, 6·1; P, 9·9. $C_{15}H_{17}O_3P$ requires C, 65·2; H, 6·2; P, 11·2%).

Diethyl vinyl phosphate was prepared by the action of carefully dried monochloroacetaldehyde on triethyl phosphite [yield, 50%; b. p. 70—72°/4 mm., n_D^{25} 1·4100; lit., b. p. 79°/6 mm.].

Kinetic Measurements.—The rate of reaction was followed by the conventional manner described previously,[1] the method of analysis depending on the particular reaction.

In the alkaline hydrolyses, aliquot parts were titrated against standard acid, bromocresol-purple being used as indicator. Since only one group is removed during hydrolysis, the rate coefficient was calculated from the general equation for a second-order process.

Reaction with Halide Ions.—The rate of neutral hydrolysis, which is accelerated by reaction with halide ions, was determined by titration of the acid released with sodium hydroxide solution, methyl-orange being used as indicator. Free iodine was liberated in the reaction with iodide ions, and the acid titration was affected as the reaction proceeded, as illustrated by the following data for the reaction of dimethyl ethylphosphonate (0·02N) at 80° with 0·2N-potassium iodide:

Time (hr.)	0	10	31	54	95	117	141
Titration (ml.) ...	0·0	0·74	1·92	2·79	3·59	3·08	1·95

In the course of the decomposition, the phosphonate or hemi-ester is probably reduced as follows: $Et{\cdot}PO(OR){\cdot}O^- + 2H^+ + 2I^- \longrightarrow Et{\cdot}P(OR){\cdot}O^- + H_2O + I_2$. The rate constants for the reaction of iodide ions with the esters were therefore determined from the initial part of the reaction. The second-order rate constant for the reaction with anion X^- was calculated from the observed first-order rate constant for the production of acid, k, by the equation

$$k = k_H + k_1 = k_H + k_2[X^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where k_1 is the pseudo-unimolecular rate constant for the reaction with the nucleophile X^-, and k_H the rate constant for the hydrolysis of the ester alone.

This equation assumes that the rate of hydrolysis of the intermediate alkyl halide is greater than that of the initial reaction, *i.e.*,

$$R'{\cdot}PO(OR)_2 + X^- \xrightarrow{\text{Slow}} R'{\cdot}PO(OR){\cdot}O^- + RX$$

$$RX + H_2O \longrightarrow ROH + H^+ + X^-$$

[14] Ford-Moore and Williams, *J.*, 1947, 1465; McCombie, Saunders, and Stacey, *J.*, 1945, 380.

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The rate constant for the hydrolysis of methyl iodide at 100° was found to be 0·71 hr.$^{-1}$, compared with the value of 4·2 × 10^{-3} hr.$^{-1}$ at 80° for the reaction between potassium iodide (0·2M) and dimethyl ethylphosphonate. The relative rates of hydrolysis of methyl chloride, bromide, and iodide confirm that the rate of the first step is considerably slower than the subsequent hydrolysis in these reactions.

Reaction with Sulphur Anions.—Acid titration could not be used to follow the reactions with thiosulphate and thiocyanate ions, and in these cases the rate was determined by following the rate of disappearance of the nucleophile. For the thiosulphate reaction, iodometric titration was used, and the reaction with thiocyanate was followed by titration with mercuric nitrate, ferric alum being used as indicator. In these cases the bimolecular rate constant is given simply by $k_2 = k_1/[X^-]$.

The stability of sodium methyl thiosulphate under the conditions of the experiment was investigated. A sample of this hemi-ester, prepared by Walden's method,[15] was recrystallised twice from water. Solutions of this salt were heated at 100° for 3 days but no iodine titrations were obtained.

The rates of alkaline hydrolysis of the esters were measured at various temperatures with the results shown in Table 3.

TABLE 3. *Hydrolysis of* 0·025N-*ester with* 0·05N-NaOH *in water.*

Et·PO(OMe)$_2$		Et$_2$PO(OMe)		Me·PO(O·CH$_2$Ph)$_2$ *		PO(OMe)$_3$			PO(OEt)$_2$·O·CH:CH$_2$	
Temp.	k_2	Temp.	k_2	Temp.	k_2	Temp.	k_2	Temp.	k_2	Temp.	k_2
80°	94·0	80°	66·0	62°	51·84	79·9°	0·556	63·8°	0·192	25°	7·20
25	0·105	25	2·16	25	9·38	72·2	0·325	60·1	0·143		

* 0·01N-Ester used. k_2 is given in l. mole^{-1} hr.$^{-1}$ units in all cases.

QUEEN MARY COLLEGE, MILE END ROAD, LONDON, E.1. [*Received, September 27th*, 1957.]

[15] Walden, *Ber.*, 1907, **40**, 3214.

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274. *Phospholipids. Part III.* The Hydrolysis of the* cis- *and the* trans-*Isomer of Glycerol* 1-(2-*Hydroxy*cyclo*hexyl Phosphate*) *and Related Compounds.*

By D. M. BROWN, G. E. HALL, and (MISS) H. M. HIGSON.

Hydrolysis by acid or alkali of glycerol 1-(*cis*-2-hydroxy*cyclo*hexyl phosphate) yields mainly 2-hydroxy*cyclo*hexyl phosphate (*ca.* 85%), whereas the *trans*-isomer gives mainly glycerol phosphate (*ca.* 75%). Rates of alkaline hydrolysis are, however, similar although appreciably greater than those found for benzyl *cis*- and *trans*-2-hydroxy*cyclo*hexyl phosphate and glycerol 1-(benzyl phosphate). In each case the reaction is of the first order in ester.

The relevance of the experiments to the chemistry of naturally occurring phosphoinositides is briefly discussed.

*myo*INOSITOL (I) occurs combined in phospholipids isolated from various sources. At least the simpler of such lipids appear [1] to be derivatives of glycerol inositol phosphate (II). We are studying the chemistry of this group and, as one objective, are seeking means of determining the position of esterification of phosphate on the *myo*inositol residue.

In Part I of this series [2] we reported the hydrolysis of the *cis*- and the *trans*-isomer of benzyl 2-hydroxy*cyclo*hexyl phosphate (III; R = CH_2Ph). Each substance gave the corresponding 2-hydroxy*cyclo*hexyl phosphate (IV) only, with acid or base, and rates were in the order *cis*- > *trans*-isomer. Evidence was adduced that hydrolysis involved the corresponding 1 : 2-*cyclo*hexylidene phosphate (V) and that therefore the hydrolytic pathway was the same as that found for other phosphodiesters carrying a vicinal hydroxyl

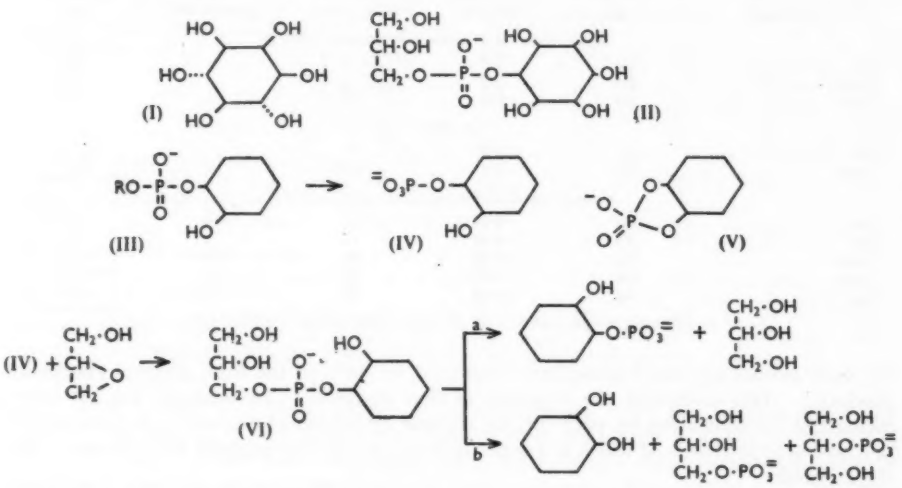
* Part II, *J.*, 1957, 2590.

[1] Folch and LeBaron, *Canad. J. Biochem. Physiol.*, 1956, **34**, 305.
[2] Brown and Higson, *J.*, 1957, 2034.

group.[3] Esters of glycerol phosphate react similarly,[4] hydrolysis *via* glycerol 1 : 2-phosphate being quantitatively the most important mode of fission (cf. refs. 5, 6; further evidence is given in the present paper). In view of this it appeared interesting to examine the hydrolysis of glycerol esters of the 2-hydroxy*cyclo*hexyl phosphates, which might be degraded by either or both of the pathways (a) and (b).

Glycidol reacted with *cyclo*hexylammonium *cis*-2-hydroxy*cyclo*hexyl hydrogen phosphate in boiling aqueous solution, and glycerol 1-(*cis*-2-hydroxy*cyclo*hexyl phosphate) (VI) was isolated as its barium salt after purification by ion-exchange chromatography.

Periodate titration showed that the product was the glycerol-1 ester (VI) containing



10% of the 2-isomer, consistently with the isomer ratio found for the reaction of glycidol with chloride ion.[7,8] The *trans*-form (VI) was similarly prepared and also found to contain 10% of the glycerol-2 ester. Owing to the solubility characteristics and instability of these esters no attempt was made to obtain the pure 1-isomers; even drying at 80° *in vacuo* caused extensive decomposition of the *trans*-form (VI),[8] the major product being tentatively identified as glycerol cyclic phosphate. It is evident, in theory, that the diester (VI) could react with a further molecule of glycidol to form a triester which would be expected to break down very readily, with phosphate migration.[9] The non-production of diglycerol phosphate, together with the high proportion of 1-isomer in the product (VI), indicates that this reaction did not take place. In initial experiments a considerably larger proportion of the 2-isomer was produced when the free hydroxy*cyclo*hexyl dihydrogen phosphate reacted with glycidol in dry dioxan.

When *cis*- and *trans*-esters (VI) were hydrolysed to completion by sodium hydroxide, paper chromatography showed that glycerol phosphate, 2-hydroxy*cyclo*hexyl phosphate,* glycerol, and *cyclo*hexanediol were produced in each case: thus hydrolysis occurred by

* Presumed to be the *cis*- and the *trans*-isomer respectively by analogy with the products formed on hydrolysis of the corresponding benzyl esters (cf. ref. 2).

[3] Brown, Magrath, Neilson, and Todd, *Nature*, 1956, **177**, 1124.
[4] Bailly and Gaumé, *Bull. Soc. chim. France*, 1935, **2**, 354.
[5] Baer and Kates, *J. Biol. Chem.*, 1948, **175**, 79; 1950, **185**, 615.
[6] Fleury, Lecocq, and Le Dizet, *Bull. Soc. chim. France*, 1956, 1193.
[7] Smith and Skyle, *Acta Chem. Scand.*, 1950, **4**, 39.
[8] A similar experience, with barium di(glycerol phosphate), has been recorded by Stockx and Vandendriessche (*Bull. Soc. chim. belges*, 1956, **65**, 919).
[9] Brown, Magrath, and Todd, *J.*, 1955, 4396.

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both paths (a) and (b). A quantitative study of the relative importance of the two pathways was made by estimating total glycerol phosphate in the hydrolysates by Burmaster's method.[10] The results are collected in Table 1. The *cis*-ester (VI) at 100° gave mainly (85%) diol phosphate (VI) and therefore decomposed predominantly by route (a), while with the *trans*-isomer route (b) was favoured (75%). At 60° the difference between the two isomers appeared as the result of one experiment to be accentuated. In the case of

TABLE 1. *Direction of hydrolysis of the glycerol* 1-(2-*hydroxy*cyclo*hexyl phosphates*).

Isomer	Cation of salt	Normality of base or acid	PO_4 (%) as glycerol phosphate	PO_4 (%) as inorg. phosphate	Time of hydrolysis (hr.)
		Hydrolysis with sodium hydroxide (100°)			
cis-	Ba	1·2	14 ± 2	—	2·0
trans-	Ba	1·2	77 ± 5	—	3·0
trans-	Na	1·0	73[a]	—	7·0
		At 60°			
cis-	Ba	1·0	11	—	24
trans-	Ba	1·0	85[b]	—	24
		Hydrolysis with hydrochloric acid (100°)			
cis-	Ba	0·44	17	8	1·5
cis-	Na	0·44	15	2	2·5
trans-	Ba	0·44	94	10	1·5
trans-	Ba	1·33	82	20	7·0
trans-	Na	0·44	89	9	2·0

[a, b] Containing 45 and 44·5% of glycerol 1-phosphate respectively.

the *trans*-isomer glycerol 1-phosphate accounted for 45% of the total glycerol phosphate produced. This confirmed the expectation that glycerol 1 : 2-phosphate was an intermediate in the hydrolysis by path (b), for alkaline hydrolysis of glycerol 1 : 2-phosphate [11] (a convenient synthesis of which is described) led to glycerol phosphate, 42% of which was the 1-isomer.

The results of acid hydrolysis of the glycerol esters (VI) (also in Table 1) were rendered less accurate by the formation of variable amounts of inorganic phosphate but, here again, the *cis*-ester (VI) yielded mainly diol phosphate (IV), whereas the *trans*-ester went almost completely to glycerol phosphate.*

These observations prompted us to study the rates of alkaline hydrolysis of the glycerol diol phosphates (VI) and, for comparison, the benzyl esters (III; R = CH_2Ph). The reactions were followed titrimetrically by determining at intervals the amount of secondary phosphoryl dissociation liberated. In view of the small amounts of the esters available no great accuracy can be claimed for the kinetic results. Hydrolyses were performed with a large excess of sodium hydroxide, and first-order rate constants were calculated with any molecularity due to alkali and water being ignored. These results, including the times of half reaction, are collected in Table 2. In the first place all the compounds are hydrolysed very much faster than dimethyl phosphate,[12] confirming our view that the reaction proceeds essentially through cyclic ester intermediates (cf. Part I). There is a small but definite catalytic effect due to barium ion, although when this ion is present it is only in very small amount relative to sodium ion (cf. refs. 6 and 12).

The benzyl, methyl, and glycerol esters of *cis*-2-hydroxy*cyclo*hexyl phosphate are all hydrolysed principally to the diol phosphate (IV), but at different rates, in the order

* *Added, February 2nd,* 1958.—Ukita, Nagasawa, and Irie [*Pharm. Bull.* (*Japan*), 1957, **5**, 121, 127] describe the synthesis of barium glycerol 1 : 2-phosphate by a method similar to that used here, and find that alkaline hydrolysis of the substance gives glycerol phosphate containing *ca.* 45% of the isomer.

[10] Burmaster, *J. Biol. Chem.*, 1946, **164**, 233.

[11] Ukita, Bates, and Carter, *ibid.*, 1955, **216**, 867; cf. Dekker and Khorana, *J. Amer. Chem. Soc.*, 1954, **76**, 3522; Khorana, Tener, Wright, and Moffatt, *ibid.*, 1957, **79**, 430.

[12] Kumamoto, Cox, and Westheimer, *ibid.*, 1956, **78**, 4858.

benzyl < methyl < glycerol. Since this order is observed in the alkaline hydrolyses of their acetates[13,14] this is consistent with P–O fission in the rate-determining step which must involve the formation, and not the hydrolysis, of the cyclic phosphate (V). For, specifically, the glycerol *cis*-ester (VI) at constant ionic strength the hydrolysis is of the first order in substrate and in hydroxide ion, and this can most simply be rationalised if it is assumed that removal of the proton from the vicinal hydroxyl group, whose pK_a value

TABLE 2. *Rates of hydrolysis of some phosphate esters.*

Compound	Cation of salt	Normality of NaOH	Approx. ionic strength	Temp.	$10^4k'$ (sec.$^{-1}$)	$t_{\frac{1}{2}}$ (hr.)
Glycerol 1-(*cis*-2-hydroxy*cyclo*hexyl phosphate)	Ba	1·0	1·0	60	115	1·9
,, ,, ,,	Ba	0·5	0·51	60	48	4·0
,, ,, ,,	Ba	1·0	1·0	40	23	8·5
,, ,, ,,	Ba	1·0	1·5	40	28	6·9[a]
,, ,, ,,	Ba	1·5	1·5	40	43	4·5
,, ,, ,,	Na	1·5	1·5	40	36	5·3
Glycerol 1-(*trans*-2-hydroxy*cyclo*hexyl phosphate)	Ba	1·0	1·0	60	89	2·2
Benzyl *cis*-2-hydroxy*cyclo*hexyl phosphate	$C_6H_{11}\cdot NH_3$	1·0	1·0	60	15	12·5
,, ,, ,,	,,	1·0	1·0	60	22	8·6[b]
Benzyl *trans*-2-hydroxy*cyclo*hexyl phosphate	,,	1·0	1·0	60	2·6	75
Methyl *cis*-2-hydroxy*cyclo*hexyl phosphate	,,	1·0	1·0	60	25	7·7
Glycerol 1-(benzyl phosphate)	,,	1·0	1·0	60	35	5·6

[a] With added NaCl. [b] With 0·5 mol. of $BaCl_2$ added per mol. of substrate.

must then exceed 14, occurs before or simultaneously with the unimolecular rate-determining step in which cyclic phosphate is formed. With $\mu = 1{\cdot}0$, we find $k = 7{\cdot}5 \times 10^6 \exp -16{,}500/RT$. Increasing ionic strength also leads to an increase in k, suggesting reaction between two negative ions in the rate-determining step, but little reliance can be put on this interpretation in view of the high values of μ involved.

Since the *cis*-ester (VI), on complete hydrolysis, gave very little glycerol phosphate, the rate of hydrolysis of glycerol 1-(benzyl phosphate) was determined and, surprisingly, was found to be greater than that of benzyl *cis*-2-hydroxy*cyclo*hexyl phosphate (III; R = CH_2Ph). Moreover, despite their mainly following different pathways, the *cis*- and the *trans*-isomer (VI) were hydrolysed at very similar rates which were also greater than those found for the benzyl esters. These observations are nevertheless self-consistent as can be shown by a calculation based on the following considerations.

Taking process (VII) as rate-determining, it seems reasonable to assume that the important, although composite, factors influencing the rate will be those concerned with (*a*) the ability of RO^- to be formed, and (*b*) the ability of the vicinal alkoxide ion to attack the phosphorus atom.[15] In comparisons of process (VII) for *cis*- and *trans*-esters (VI), factor (*a*) is constant, whilst relative effects of factor (*b*) are obtained by comparing rates for the benzyl ester of *cis*- and of *trans*-2-hydroxy*cyclo*hexyl phosphate (III; R = CH_2Ph). From the values in the Tables, the partial rate constant ($\times 10^6$) at 60° of process (VII) for *cis*-ester (VI) is $89 \times 115/100 = 102{\cdot}3$; and, when the rates for the two benzyl esters are taken into account, the expected partial rate constant of process (VII) for the *trans*-isomer (VI) is $102{\cdot}3 \times 2{\cdot}6/15 = 17{\cdot}7$. Hence the percentage of glycerol phosphate in the hydrolysate of *trans*-ester (VI) should be $(89 - 17{\cdot}7)/89 \times 100 = 80\%$, in good agreement with the experimental value of 85%.

[13] Newling and Hinshelwood, *J.*, 1936, 1359; Tommila, *Ann. Acad. Sci. Fennicae*, 1941, *A*, **59**, No. 4, 3; *Chem. Abs.*, 1944, **38**, 6172.

[14] Meyer, *Z. phys. Chem.*, 1910, **67**, 257; Jellinek, *Rev. Pure Appl. Chem.*, 1952, **2**, 147.

[15] Cf. Hine, "Physical Organic Chemistry," McGraw-Hill Co. Inc., New York, 1956, p. 274, for a corresponding discussion of the alkaline hydrolysis of carboxylic esters.

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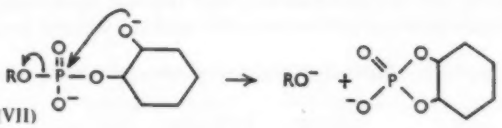
It appears that the greater rates of hydrolysis of the glycerol diol phosphates (VI) are dependent on a special factor, *viz.*, the presence of two neighbouring hydroxyl groups. Hydrogen-bonding may then assist reaction by stabilising the ejected anion or by facilitating attack on the phosphorus atom.[16] It may be significant in this connection that



(VII)

glycerol 2-(methyl phosphate) is hydrolysed considerably faster than the 1-isomer.[6] We are investigating in more detail the structural effects which influence rate and direction of cleavage in these and related compounds.

The proportions of the cleavage products from the hydrolysis of the glycerol diol phosphates (VI) might suggest that the only factor influencing the hydrolysis of a phospholipid based on glycerol inositol phosphate (II) would be the *cis*- or *trans*-orientation of the neighbouring hydroxyl groups. If this is so, the predominant direction of breakdown should give information about the position of linkage of the glycerol phosphate residue to the *myo*inositol ring. Certain recorded observations [1,17] could be taken to indicate that some phosphoinositides do behave analogously to the synthetic esters (VI): however, taking our experiments as a whole we do not feel justified in drawing any definite conclusion without further experimental evidence. On the other hand the present work shows that the non-appearance of glycerol phosphate or inositol phosphate should not be assumed to indicate the absence of structure (II) in the parent phosphoinositide. Finally, it must be expected that any inositol phosphate fraction isolated from an acid or alkaline hydrolysate will be a mixture of (positional) isomers.

Experimental

The R_F values, which varied by 0·1 unit in different runs, were taken from chromatograms in which Whatman No. 1 paper and the propan-2-ol–ammonia–water (7 : 1 : 2) solvent system were used.

Barium Glycerol 1-(cis-2-*Hydroxy*cyclo*hexyl Phosphate*).—A solution of *cyclo*hexylammonium *cis*-2-hydroxy*cyclo*hexyl hydrogen phosphate (1·0 g.) and glycidol (1 c.c.; 4·6 mol.) in water (35 c.c.) was boiled under reflux for 6 hr. Paper chromatography indicated 70% conversion of the phosphate into a single phosphorus-containing product (R_F 0·60). After dilution to 80 c.c. and adjustment to pH 8—9, the solution was run on to a column (7·5 × 1·0 cm.) of Dowex-2 resin (formate form). The column was washed with water (500 c.c.), then 0·01N-formic acid (200 c.c.), and the product was eluted with 0·05N-formic acid, fractions of about 200 c.c. being collected. These were separately evaporated very carefully under reduced pressure to 5 c.c., then neutralised with barium hydroxide, and a little barium carbonate was added. Fractions containing only the product were combined and evaporated as above, and the colourless solid residue was dried over calcium chloride. This material was extracted with ethanol (2 × 15 c.c.), the extract evaporated, the residue dissolved in a little ethanol, and the product precipitated by addition of pure dry acetone. Several similar reprecipitations gave the pure *product* as a colourless hygroscopic powder (640 mg.), which gave one spot (R_F 0·55) (Found, in material dried at 50° over P_2O_5 at 1 mm. for 7 hr.: C, 27·7; H, 6·1; P, 7·5 $C_{18}H_{36}O_{14}P_2Ba,6H_2O$ requires C, 27·6; H, 6·1; P, 7·9%).

Periodate titrations showed an uptake of 0·9 ± 0·04 mol. of oxidant per atom of P, indicating the presence in the product of *ca.* 10% of the glycerol-2 isomer.

Barium Glycerol 1-(trans-2-*Hydroxy*cyclo*hexyl Phosphate*).—The preparation was carried out as described for the *cis*-isomer except that *cyclo*hexylammonium *trans*-2-hydroxy*cyclo*hexyl hydrogen phosphate (1·03 g.) was employed. The *product* was obtained as a very hygroscopic

[16] Henbest, *J.*, 1957, 1965.
[17] Hawthorne and Hawthorne in Popjak and LeBreton's "Biochemical Problems of Lipids", Butterworths, London, 1956, p. 104.

colourless, amorphous powder (350 mg.), R_F 0·55 (Found, in material dried *in vacuo* over $CaCl_2$ and SiO_2 gel: C, 31·4; H, 6·0; P, 8·6; Ba, 20·2. $C_{18}H_{36}O_{14}P_2Ba,H_2O$ requires C, 31·2; H, 5·5; P, 8·9; Ba, 19·8%).

Periodate titrations showed an uptake of 0·89 ± 0·04 mol. of oxidant per atom of P, indicating the presence of *ca.* 10% of the glycerol-2 isomer.

Drying the substance at 80°/1 mm. for 12 hr. caused extensive decomposition, the major phosphorus-containing product corresponding to glycerol cyclic phosphate on chromatograms and electrophoretograms.

For certain hydrolytic experiments the above barium salt was converted into the sodium salt. The barium salt (25·05 mg.) in water (2 c.c.) was treated with sodium sulphate decahydrate (12·5 mg., 1·07 mol.) in water (2 c.c.). Precipitated barium sulphate was removed by centrifugation and the aqueous solution used as such. The sodium salt of the *cis*-isomer was prepared similarly.

*Hydrolysis of Above Glycerol Hydroxy*cyclo*hexyl Phosphates.*—(a) *Direction of cleavage.* The appropriate salt (7—10 mg.) was dissolved in the hydrolysis solution (3 c.c.; see Table 1) and boiled under reflux in a Pyrex tube. Blanks, to which no organic phosphate was added, were run concurrently. After cooling, and in the case of alkaline hydrolyses after neutralisation with 10N-sulphuric acid, the solutions were diluted to 25 c.c. Aliquot parts were removed for determination of total phosphate [18] (2 c.c.) and for total glycerol phosphate (5 c.c. and 2 c.c. for the *cis*- and the *trans*-isomer respectively) by the following modification of Burmaster's method.[19] The aliquot parts were put in boiling tubes, 0·05M-sodium metaperiodate (1 c.c.) and 10N-sulphuric acid (1 c.c.) were added, and the solution was heated in boiling water for 1 hr., solution volumes being kept at 5—7 c.c. with distilled water. After cooling and addition of 4% sodium sulphite (1 c.c.) to destroy excess of periodate, amidol (2 c.c.) and molybdate (1 c.c.) were added, the solution was diluted to 25 c.c., and the optical density at 750 mμ determined after exactly 20 min. as in Allen's method for inorganic phosphate.[18] This gave a measure of glycerol phosphate plus inorganic and acid-labile phosphate. The sum of the last two, negligible in the alkaline hydrolyses, was obtained by carrying out the above estimation but without addition of periodate. The results are recorded in Table 1.

In two experiments, *viz.*, the hydrolysis by N-sodium hydroxide at 100° and 60° of barium glycerol 1-(*trans*-2-hydroxy*cyclo*hexyl phosphate), glycerol 1-phosphate was determined in the hydrolysate by diluting an aliquot part (2 c.c.) to 5 c.c., adding 0·05M-sodium periodate (1 c.c.) and 0·1N-sulphuric acid (1 c.c.), and setting the whole aside for 10 min. at room temperature. 4% Sodium sulphite solution (1 c.c.) and 10N-sulphuric acid (1 c.c.) were added and the solution was heated at 100° for 1 hr. Inorganic phosphate was then estimated as above and gave a direct measure of the glycerol 1-phosphate content of the original solution. This was found to be, in each case, 45% of the total glycerol phosphate.

(b) *Rates of hydrolysis.* Solutions of the substances (15—30 mg.) in aqueous sodium hydroxide (6·6 c.c.), together with blanks containing no organic phosphate, were heated in closed Polythene tubes supported in brass cylinders in the thermostat, and aliquot parts (1 c.c.), usually 6 per run, were withdrawn at intervals. These were brought to pH 2—3 with dilute hydrochloric acid and then titrated over the pH range 4·9—8·4 with carbonate-free 0·025N-sodium hydroxide, rigorous conditions being maintained for the exclusion of carbon dioxide. A direct-reading pH meter was used. The volume of alkali required by the blank was subtracted from the corresponding figure for the hydrolysate. For 2-hydroxy*cyclo*hexyl phosphate and glycerol 1-phosphate under similar conditions, it was found that the corrected alkali titre was then proportional to the amount of secondary phosphoryl dissociation, although the absolute values appeared slightly in error.

The first-order rate constants (k') and times of half-hydrolysis ($t_{\frac{1}{2}}$) were calculated and are recorded in Table 2, together with the corresponding values for other related substances.

cyclo*Hexylammonium* cis-2-*Hydroxy*cyclo*hexyl Methyl Phosphate.*—*cyclo*Hexylammonium *cis*-2-hydroxy*cyclo*hexyl hydrogen phosphate (200 mg.) in methanol (10 c.c.) was treated with ethereal diazomethane until the solution remained yellow. Next morning solvent was removed and the *product* crystallised from ethanol–ethyl acetate, as needles (110 mg.), m. p. 188—189·5°, R_F 0·60 (Found, in material dried over P_2O_5 at 70°/0·1 mm.: C, 50·4; H, 9·4; N, 4·75. $C_{13}H_{28}O_5NP$ requires C, 50·5; H, 9·2; N, 4·5%).

cyclo*Hexylammonium* trans-2-*Hydroxy*cyclo*hexyl Methyl Phosphate.*—This was made as

[18] Allen, *Biochem. J.*, 1940, **34**, 858.

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above but from *cyclo*hexylammonium *trans*-2-hydroxy*cyclo*hexyl phosphate. The *product* formed needles, m. p. 183—185° after two recrystallisations, R_F 0·63 (Found: C, 50·4; H, 9·3; N, 4·4%).

Di(cyclo*hexylammonium*) *Glycerol* 1-*Phosphate*.—The reaction between glycidol and disodium hydrogen phosphate in water was used but, instead of forming the barium or calcium salt according to Bailly,[19] the reaction mixture was treated first with excess of barium hydroxide to remove phosphate and then with Dowex-50 resin (H form) to remove barium ion. The solution was brought to pH 10 with *cyclo*hexylamine and evaporated under reduced pressure. Recrystallisation of the residue from ethanol–ethyl acetate gave the *product* in fine needles, m. p. 145—150° (Found: C, 48·2; H, 9·6; N, 7·7. $C_{15}H_{35}O_6N_2P$ requires C, 48·6; H, 9·5; N, 7·6%).

The salt consumed 0·98 mol. of periodate per atom of P, on oxidation.

cyclo*Hexylammonium Glycerol* 1-(*Benzyl Phosphate*).—Barium glycerol 1-phosphate (2·3 g.) was shaken with a little Dowex-50 resin (H form) and the solution poured on to a short column of the same resin. Effluent and washings were neutralised with *cyclo*hexylamine (1 c.c., 1 mol.), and the solution was evaporated to dryness. The half-salt was dissolved in ethanol (20 c.c.), and the solution treated with phenyldiazomethane (from 2·4 g. of benzaldehyde hydrazone) in ether. Next morning most of the solvent was evaporated water and chloroform were added, and the aqueous layer (20 c.c.) extracted twice with chloroform. Evaporation of the aqueous solution gave an oil which crystallised from ethanol–ethyl acetate. Two recrystallisations gave the *ester* as fine needles, m. p. 126°, R_F 0·63 (Found: C, 52·8; H, 8·4; N, 4·0. $C_{16}H_{28}O_6NP$ requires C, 53·2; H, 7·8; N, 3·9%).

Brucine Glycerol 1 : 2-*Phosphate*.—An aqueous solution of sodium glycerol 2-phosphate (0·4 g.) was passed through a column of Dowex-50 resin (H form), and the acidic effluent and washings were evaporated to dryness below 40°. The colourless oil was dissolved in dimethylformamide (10 c.c.), and di*cyclo*hexylcarbodi-imide (0·3 g.) in the same solvent (10 c.c.) was added. Di*cyclo*hexylurea separated almost immediately. Paper chromatography showed that, after 12 hr., the required product was present as the major component, contaminated with a little starting material. After the mixture had been brought to pH 10 with dilute ammonia and set aside for 0·5 hr., di*cyclo*hexylurea was filtered off and solvents were removed at 1 mm. The oily residue was purified by chromatography on a cellulose column (30 × 3·5 cm.) with propan-2-ol–ammonia (*d* 0·88)–water (40 : 1 : 14) as developing solvent. The required fractions, located by paper chromatography, were evaporated under reduced pressure, the residue was dissolved in water, and the solution passed through a Zeo-Karb 215 (H form) column. The effluent was neutralised with brucine in methanol, then evaporated to dryness, and the crude product (310 mg.) purified by two recrystallisations from ethanol. *Brucine glycerol* 1 : 2-*phosphate* crystallised as a monohydrate in needles (Found, in material dried at 50°/0·5 mm.: C, 55·1; H, 6·4; N, 5·1. $C_{26}H_{32}O_8N_2P,H_2O$ requires C, 55·1; H, 6·2; N, 5·0%).

The substance gave one phosphate-positive spot (R_F 0·4) on a paper chromatogram. Electrometric titration showed the absence of secondary phosphoryl dissociation. After this experiment had been done, Khorana *et al.*[11] mentioned, without experimental details, that the cyclic phosphate may be prepared by the above method.

Hydrolysis of Glycerol 1 : 2-*Phosphate*.—In a qualitative experiment, heating the brucine salt at 100° in N-sodium hydroxide caused complete conversion into glycerol phosphate in less than 5 min., as shown by paper chromatography. That the glycerol phosphate was a mixture of the 1- and the 2-isomer was shown by periodate titration. The brucine salt (50 mg.) was dissolved in N-sodium hydroxide (20 c.c.) and freed from brucine by chloroform-extraction, and the hydrolysis completed on the water-bath. Periodate titration and phosphorus estimation after 2 and 3 hr. showed an uptake of 0·42 mol. of oxidant per atom of P, corresponding to a 42 : 58 ratio of the 1- and 2-isomers of glycerol phosphate.

Our thanks are offered to Sir Alexander Todd, F.R.S., for his help and encouragement. A Department of Scientific and Industrial Research Award (to G. E. H.) is gratefully acknowledged.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 4th*, 1957.]

[19] Bailly, *Ann. Chim.* (*France*), 1916, **6**, 123.

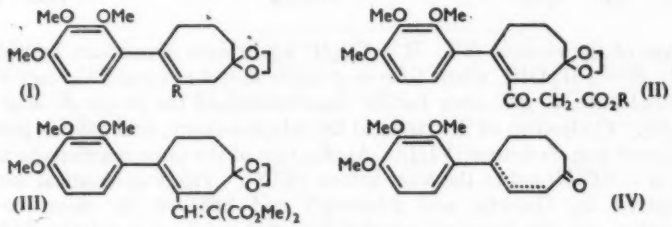
275. *Syntheses in the Colchicine Series. Part II.* Some Tricyclic Models.*

By H. J. E. Loewenthal.

The preparation of several compounds based on dibenzo[*a,c*]*cyclo*heptatriene is described, and some aspects of their stereochemistry and of that of intermediate compounds are discussed.

In Part I the preparation of 6 : 6-ethylenedioxy-2-(2 : 3 : 4-trimethoxyphenyl)*cyclo*hept-1-enecarboxylic acid (I; R = CO_2H), a potential intermediate for the synthesis of colchicine, was described. The primary intention was to use the carboxyl group as a starting point for constructing the elements of ring B of the alkaloid. Several ways were explored to extend a chain incorporating a potential acetamido-function while retaining the *cyclo*heptene double bond, but none of these led to a useful ring-closure product.

For example, the acid (I; R = CO_2H) was treated with methyl-lithium to give the ketone (I; R = Ac); carboxylation of this under forcing conditions with ethyl or methyl carbonate led to the keto-esters (II; R = Et or Me), which were found unsuitable for further transformations. Alternatively, the ester (I; R = CO_2Me) was reduced to the alcohol (I; R = CH_2·OH) which was smoothly oxidised with manganese dioxide to the unsaturated aldehyde (I; R = CHO). This with dimethyl malonate afforded the unsaturated diester (III); addition of nucleophilic reagents to its αβ-double bond with subsequent cyclisation to the aromatic ring also gave unpromising results. Finally, attempted decarboxylation of the ketal-acid (I; R = CO_2H) or of its derived keto-acid in



order to give a 4-(2 : 3 : 4-trimethoxyphenyl)*cyclo*heptenone (IV) or its ketal (which might have been a suitable starting material for attachment of a side-chain by Michael addition) failed; the only product obtained was 7 : 8-dimethoxy-4′-oxo*cyclo*hepteno(2′ :-1′-3 : 4)-coumarin (see Part I) through elimination of methanol, even when basic conditions (copper chromite in quinoline) were used.

It was decided to continue this work using a saturated system by reduction of the double bond in the alicylic ring of the acid (I), notwithstanding the ensuing stereochemical complications; the easily accessible 2-(2 : 3 : 4-trimethoxyphenyl)*cyclo*hex-1-enecarboxylic acid (V) was taken as a model compound.

The double bond in the latter resisted catalytic reduction in non-acidic solvents, but lithium in liquid ammonia in the absence of alcohol gave in high yield a saturated acid (VI; R = CO_2H); this was believed to be the *trans*-epimer, until it was found that the methyl ester (VI; R = CO_2Me) could be epimerised in high yield (with sodium methoxide in methanol [1]) to give, after aqueous hydrolysis, the epimeric acid (VII; R = CO_2H).

Both in the lithium–ammonia reduction of acid (V) and in the epimerisation of ester (VI; R = CO_2Me) the step which determines the stereochemistry is the addition of a proton to the same carbanion, that nearest to the carboxyl group. In the epimerisation

* Part I, *J.*, 1953, 3962.

[1] Compare the epimerisation of *cis*-2-phenyl*cyclo*hexanecarboxylic acid; Alder, Vagt, and Vogt, *Annalen*, 1949, **565**, 135.

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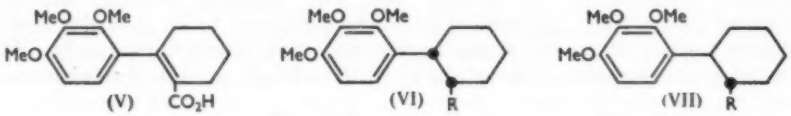
this step must be thermodynamically controlled to lead to a stable *trans*-1 : 2-disubstituted *cyclo*hexane derivative. Conversely in the lithium–ammonia reduction proton addition appears to be kinetically controlled to give the unstable *cis*-epimer. This case therefore does not coincide with Barton and Robinson's views [2] on the stereochemistry of similar reductions. It must be noted that recently published work by a number of authors [3, 4, 5] on the metal–ammonia reduction of conjugated double bonds (all of them tetrasubstituted) reports the formation of an unstable *cis*-epimer as the main product. This has been explained by assuming that in the initially formed dianion the more important factor is not a favourable configuration of the anion on the carbon adjacent to the activating group (carbonyl, aryl), but greater accessability (equatorial approach) of the proton to that carbanion. In the reduction of an α-octalone a *cis*-α-decalone would then be the initial product (in the case mentioned by Birch *et al.*[3] epimerisation to the *trans*-ketone was effected simply by chromatography on alumina). Perusal of the experimental parts of the papers cited by Barton *et al.*[2] in support of their views in the steroid and triterpenoid field shows that in each case which appeared to lead to the formation of a *trans*-α-decalone the reaction product from metal–ammonia reduction was either chromatographed on alumina or subjected to more drastic alkaline treatment before being identified. Such results may therefore be misleading and perhaps should be re-investigated.



Reduction of the *cis*-acid (VI; R = CO_2H) by lithium aluminium hydride gave the alcohol (VI; R = CH_2·OH), whose toluene-*p*-sulphonate was caused to react with di-*tert.*-butyl sodiomalonate, to give after further transformations the propionic acid (VI; R = $[CH_2]_2$·CO_2H). Cyclisation of the last acid by polyphosphoric acid gave in good yield the seven-membered ring *cis*-ketone (VIII). Application of the same reactions to the epimeric acid (VII; R = CO_2H) led to the *trans*-ketone (XIX). This was identical with the compound prepared by Gutsche and Fleming [6] and believed by them to have the *cis*-configuration, on the basis of usually accepted rules of catalytic hydrogenation, in this case of the unsaturated ester precursor of this ketone, and on the basis of melting-point relationships of similar *cis*- and *trans*-epimers. Both ketones (VIII and XIX) were easily converted into the corresponding *cyclo*alkenes (IX and XX respectively), by reduction with sodium borohydride to the corresponding alcohols which were dehydrated without purification with naphthalene-β-sulphonic acid in benzene.

Oxidation of the *cyclo*alkene (IX) with selenium dioxide in pyridine gave a mixture, separable by chromatography. The main products were the unsaturated alcohol (X) and the unsaturated ketone (XIII) which was itself obtained from (X) by oxidation with manganese dioxide. Minor products are formulated as: the ketone (XI) [possibly formed as a result of an allylic shift in (X)] since on catalytic hydrogenation it gave the original ketone (VIII), although the αβ-unsaturated ketone characteristics of both its infrared and ultraviolet spectra were abnormally weak; and a compound $C_{18}H_{22}O_5$ [possibly (XII)] whose infrared and ultraviolet spectra were similar to those of (XIII) and whose analysis showed the presence of an additional hydroxyl group.

Catalytic reduction of the unsaturated ketone (XIII) gave the saturated *cis*-ketone

[2] Barton and Robinson, *J.*, 1954, 3045.
[3] Birch, Smith, and Thornton, *J.*, 1957, 1339.
[4] Zimmerman, *J. Amer. Chem. Soc.*, 1956, **78**, 1168.
[5] Johnson, Ackerman, Eastham, and Dewalt, *ibid.*, p. 6302.
[6] Gutsche and Fleming, *J. Amer. Chem. Soc.*, 1954, **76**, 1771.

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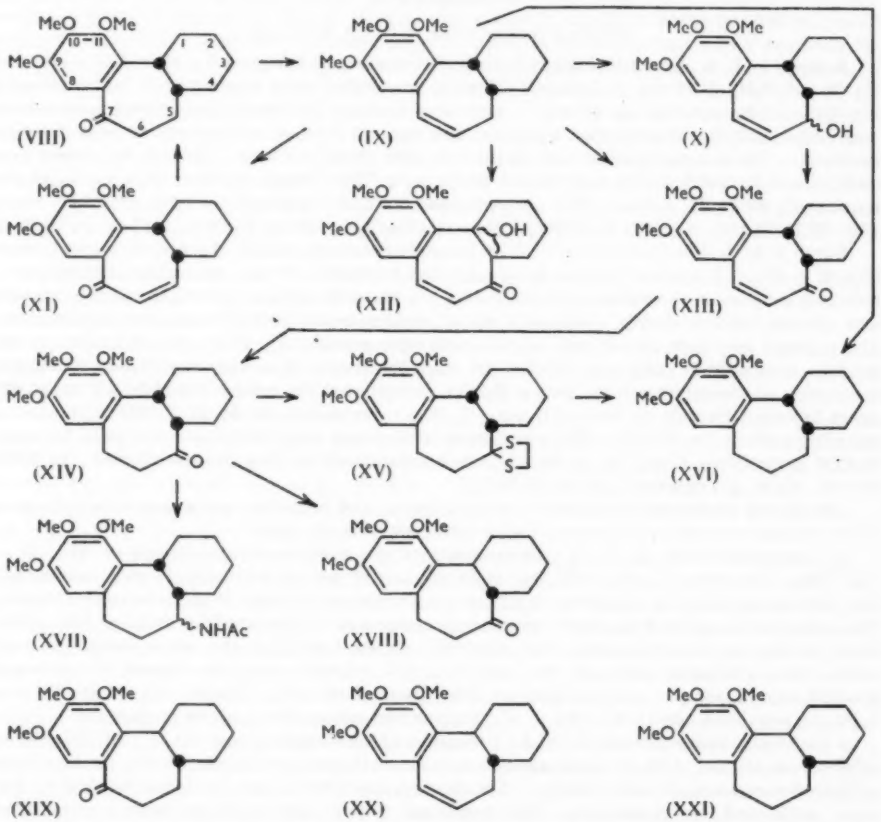
(XIV) which was epimerised to its *trans*-epimer (XVIII) to the extent of about 35—45% by either acid or base. Surprisingly, the unsaturated ketone (XIII) could not be epimerised. Further, the olefin (XX) was inert to the action of selenium dioxide under the conditions used for the oxidation of its epimer (IX). These phenomena became clearer to understand when models of these two olefins were examined. These show that only with a *cis*-fusion, such as exists in (IX), is it possible for the olefinic double bond to be coplanar with the aromatic ring. A confirming fact is the difference in light absorption between these two compounds: (IX) $\lambda_{max.}$ 263 mμ, ε 13,100; (XX) $\lambda_{max.}$ 260 mμ, ε 8950; and presumably coplanarity in (IX) explains the resistance of the unsaturated *cis*-ketone (XIII) to epimerisation, which would decrease the resonance of the extended conjugated system (a factor which would disappear on reduction of the double bond).

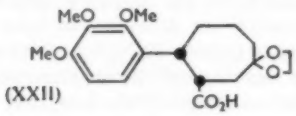


Reduction of the oxime of the ketone (XIV) by lithium aluminium hydride, followed by acetylation, gave the amide (XVII) as a mixture of two substances, possibly epimeric at $C_{(5)}$, thus completing the actual construction of a ring B analogue of colchicine.

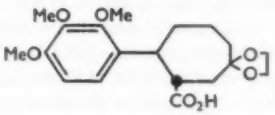
In order to show that in the route (IX) ⟶ (XIV) the original *cis*-configuration at the ring junction had been retained, the ketone (XIV) was converted into the ethylene dithioketal (XV) and thence into the saturated compound (XVI) identical with the product of catalytic hydrogenation of the *cyclo*heptene (IX).

Reduction with lithium and liquid ammonia, was then applied to the unsaturated acid (I; R = CO_2H), with similar results. The main product was a low-melting saturated acid

(XXII), accompanied by a higher-melting epimer (XXIII). The ester of the latter was obtained in practically theoretical yield by epimerising the methyl ester of the former. While little is yet known of conformational preferences in a seven- as compared with a six-membered ring, the acids (XXII) and (XXIII) may be reasonably formulated as the *cis*- and the *trans*-epimer, respectively.



(XXII)



(XXIII)

Experimental

Infrared spectra refer to $CHCl_3$ solutions.

*2-Acetyl-1-(2 : 3 : 4-trimethoxyphenyl)-4 : 4-ethylenedioxy*cyclo*heptene* (I; R = Ac).—The acid (I; R = CO_2H) (3·65 g.), in benzene (25 ml.), was added with stirring at 0° to an ethereal N-solution of methyl-lithium (30 ml.). After several hours' stirring at room temperature water was added and the mixture was separated into neutral (2·83 g.) and recovered acid (0·88 g.) fractions. The neutral fraction was distilled at 200° (bath)/0·01 mm., to give the *ketone* as a clear oil which solidified after several months (m. p. *ca.* 70°) (Found: C, 66·4; H, 7·6. $C_{20}H_{28}O_6$ requires C, 66·3; H, 7·2%). The *semicarbazone*, needles from aqueous methanol, had m. p. 170—172° (Found: C, 60·2; H, 6·25; N, 9·8. $C_{21}H_{29}O_6N_3$ requires C, 60·1; H, 7·0; N, 10·0%).

Ethyl β-[6 : 6-*Ethylenedioxy*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*hept*-1-*enyl*]-β-*oxopropionate* (II; R = Et).—The above ketone (2·2 g.) in ethyl carbonate (10 ml.) was added dropwise to a refluxing suspension of sodium hydride (0·16 g.) in the same solvent (10 ml.), and the mixture was refluxed for 3 hr. during which *ca.* 5 ml. of liquid were distilled off through a short column. The mixture was then cooled and diluted with light petroleum. The sodio-derivative of the product crystallised; this was filtered off and cautiously dissolved in aqueous methanol. Saturation of the solution with carbon dioxide precipitated the β-*keto-ester* (1·50 g.), m. p. 99° (from hexane) (Found: C, 64·2; H, 7·5. $C_{23}H_{30}O_8$ requires C, 63·6; H, 7·0%). The corresponding *methyl ester* (II; R = Me) was formed in the same way, though in lower yield, by using methyl carbonate; it had m. p. 85—86° after crystallisation from hexane (Found: C, 62·5; H, 6·6. $C_{22}H_{28}O_8$ requires C, 62·8; H, 6·7%).

Attempted formation of an amino-crotonic ester, and reductive amination with hydrogen, Raney nickel catalyst, and ammonia failed with each of these esters.

*2-Hydroxymethyl-1-(2 : 3 : 4-trimethoxyphenyl)-4 : 4-ethylenedioxy*cyclo*heptene* (I; R = CH_2·OH).—The ester (I; R = CO_2Me) (4·24 g.), in dry tetrahydrofuran (15 ml.), was added with stirring at −15° to a suspension of lithium aluminium hydride (0·50 g.) in ether (15 ml.). The solution was allowed to attain room temperature and then stirred for another 2 hr. The usual working-up (decomposition with Rochelle salt solution) gave the crude *alcohol* (4·20 g.) which was sufficiently pure for the next step (its infrared spectrum showed no carbonyl absorption); a sample was distilled at 200° (bath)/0·01 mm. (Found: C, 64·8; H, 8·0. $C_{19}H_{26}O_6$ requires C, 65·1; H, 7·5%). Crystalline derivatives could not be prepared.

*4 : 4-Ethylenedioxy-2-formyl-1-(2 : 3 : 4-trimethoxyphenyl)*cyclo*heptene* (I; R = CHO).—The above crude alcohol (3·50 g.) was shaken in acid-free carbon tetrachloride (60 ml.) for 4 hr. with activated manganese dioxide [7] (22 g.). The mixture was filtered and the residue washed several times with acid-free chloroform. The combined filtrate and washings were concentrated *in vacuo*, to give the crude *aldehyde*, which crystallised (2·83 g.) on trituration with light petroleum. Recrystallisation from hexane gave needles, m. p. 91° (Found: C, 65·4; H, 7·2. $C_{19}H_{24}O_6$ requires C, 65·5; H, 6·9%). The infrared spectrum showed a strong band at 6·0 μ. The *semicarbazone* had m. p. 212—213° (from aqueous methanol) (Found: C, 59·8; H, 6·7; N, 10·3. $C_{20}H_{27}O_6N_3$ requires C, 59·2; H, 6·7; N, 10·4%).

Dimethyl α-[6 : 6-*Ethylenedioxy*-2-(2 : 3 : 4-*trimethoxyphenyl*)-cyclo*hept*-1-*enylmethylene*]-*malonate* (III).—The above aldehyde (5·0 g.), dimethyl malonate (4·55 g.), piperidine (5 drops), and acetic acid (5 drops), in benzene (70 ml.), were refluxed under an azeotropic water-separator for 10 hr. The solution was cooled, washed with ice-cold dilute acetic acid, sodium hydrogen

[7] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1094.

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carbonate solution, and water, and the solvent removed after drying. The residue was heated at 100°/0·01 mm., to remove excess of malonic ester. It then crystallised very slowly on trituration with light petroleum, to give the unsaturated *diester* (6·30 g.), m. p. 70—75°. This recrystallised with great difficulty from aqueous methanol to give prisms, m. p. 83° (Found: C, 61·9; H, 6·4; OMe, 34·2. $C_{24}H_{36}O_9$ requires C, 62·3; H, 6·5; OMe, 33·5%). The infrared spectrum showed a strong band at 5·82 μ.

Addition of cyanide ion to this unsaturated ester,[8] followed by treatment of the crude product with polyphosphoric acid under various conditions, gave mostly intractable tars from which a very small amount of a crystalline *substance*, m. p. 252° (decomp.) (from acetone), was isolated (Found: C, 66·8; H, 6·2; N, 3·9. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·5; N, 3·9%). The infrared spectrum showed a strong band at 5·87 μ and a weak band at 3·16 μ (possibly N–H frequency); this substance was not further investigated.

cis-2-(2 : 3 : 4-*Trimethoxyphenyl*)cyclo*hexanecarboxylic Acid* (VI; R = CO_2H).—The unsaturated acid [9] (V) (finely powdered; 11·0 g.) was stirred in liquid ammonia (*ca.* 600 ml.) until most of it dissolved. Lithium was added in grain-sized pieces until a blue colour persisted for more than 1 min.; the colour was then immediately discharged by addition of solid ammonium chloride. The addition took about 1 hr. and about 2—3 g.-equivs. of the metal (0·6—0·7 g.) were required. The ammonia was allowed to evaporate, finally on the steam-bath, and the solid residue was dissolved in water. The solution was saturated with sodium chloride, washed with ether, and acidified. The *acid* which separated crystallised on trituration and recrystallised from aqueous methanol as needles (8·05 g.), m. p. 127—128° (Found: C, 65·0; H, 7·65; OMe, 31·5. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5; OMe, 31·6%). The *methyl ester*, prepared with diazomethane, had m. p. 69·5—70° (needles from pentane at −10°) (Found: C, 66·2; H, 7·9. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·85%).

Hydrogenation of the acid (V) with Adams catalyst in ethanol, or reduction with Raney nickel alloy and alkali, was unsuccessful, the compound being recovered.

cis-1-*Hydroxymethyl*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*hexane* (VI; R = CH_2·OH).—The above saturated acid (17·82 g.), in dry tetrahydrofuran (50 ml.), was added with stirring to a suspension of lithium aluminium hydride (5·0 g.) in ether (50 ml.), and the mixture was refluxed for 4 hr., then worked up in the usual way; the ether and tetrahydrofuran were removed *in vacuo* and the oil taken up in benzene. The organic layer was washed with 10% sodium hydroxide solution, and then water, and dried. Removal of the solvent gave the crude *alcohol* (15·76 g.), which was used without purification. A sample was evaporatively distilled at 180° (bath)/0·01 mm. (Found: C, 68·2; H, 8·4. $C_{16}H_{24}O_4$ requires C, 68·5; H, 8·6%). The *p-nitrobenzoate* formed yellowish needles (from hexane), m. p. 107° (Found: C, 64·8; H, 6·2; N, 3·5. $C_{23}H_{27}O_7N$ requires C, 64·3; H, 6·3; N, 3·3%).

β-[cis-2-(2 : 3 : 4-*Trimethoxyphenyl*)cyclo*hexyl*]*propionic Acid* (VI; R = $[CH_2]_2$·CO_2H).—The above crude alcohol (20·5 g.) was dissolved in dry pyridine (56 ml.), and the solution was distilled to remove *ca.* 5 ml. of solvent. After cooling to 0° toluene-*p*-sulphonyl chloride (14·6 g.) was added with shaking. The solution was left at 0° overnight, then water, containing the theoretical amount of potassium hydrogen carbonate, was added. The oil which separated was twice extracted with ether–benzene. The extract was washed successively with water, ice-cold dilute hydrochloric acid (twice), water, dilute sodium carbonate solution, and sodium chloride solution, and dried. Removal of the solvents in *vacuo* left the crude oily toluene-sulphonate (31·3 g.). This, dissolved in the minimum amount of dry benzene, was added to a suspension of di-*tert.*-butyl sodiomalonate, prepared from the ester (31·5 g.) and sodium hydride (3·1 g.) in dry benzene (100 ml.). The mixture was refluxed for 30 hr. Water was then added to dissolve the precipitated solids, and to the dried benzene layer toluene-*p*-sulphonic acid (1·0 g.) was added. The solution was heated under reflux until gas evolution had ceased (3—4 hr.), then washed with the minimum amount of water, and dried again and the benzene was removed *in vacuo*. The residue was heated at 170—200° until no more carbon dioxide was evolved (10 min.), cooled, and taken up in ether. The ether solution was extracted several times with 10% sodium carbonate solution. Acidification of the extracts liberated the *acid* as an oil (13·5 g.) which was isolated with benzene. A sample was evaporatively distilled at 200° (bath)/0·01 mm. (Found: C, 67·3; H, 8·2. $C_{18}H_{26}O_5$ requires C, 67·1; H, 8·1%).

cis-1 : 2 : 3 : 4 : 4*a* : 5 : 6 : 11*b*-*Octahydro*-9 : 10 : 11-*trimethoxy*-7-*oxodibenzo*[a,c]cyclo*heptatriene*

[8] Allen and Johnson, *Org. Synth.*, 1950, **30**, 83.
[9] Boekelheide and Pennington, *J. Amer. Chem. Soc.*, 1952, **74**, 1558.

XUM

(VIII).—To the above crude acid (5·00 g.) polyphosphoric acid, prepared from 85% orthophosphoric acid (38 ml.) and phosphoric oxide (60 g.), was added, and the resulting red solution was heated at 75—85° for 1 hr. with occasional shaking. Ice was added and the solution was extracted several times with methylene chloride–ether. The extracts were washed with 10% sodium hydroxide solution and water. Removal of solvents from the dried extract left a residue (4·63 g.) which solidified and recrystallised from benzene–methanol, to give the *ketone* (3·85 g.), needles, m. p. 107° (Found: C, 71·2; H, 7·7. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%). The 2 : 4-*dinitrophenylhydrazone* formed orange-red leaflets, m. p. 222—223° (Found: C, 58·8; H, 5·8; N, 11·5. $C_{24}H_{28}O_7N_4$ requires C, 59·5; H, 5·8; N, 11·6%); this m. p. was obtained only after slow recrystallisation from benzene–*cyclo*hexane; recrystallisation from chloroform–ethanol or from ethyl acetate–ethanol always gave low-melting mixtures of polymorphic forms.

trans-2-(2 : 3 : 4-*Trimethoxyphenyl*)cyclo*hexanecarboxylic Acid* (VII; R = CO_2H).—The *cis*-epimer (VI; R = CO_2H) (10 g.) was treated with an excess of ethereal diazomethane. To the resulting methyl ester, obtained after removal of ether *in vacuo*, a 15% solution of sodium methoxide in methanol (75 ml.) was added and the whole was refluxed for 12 hr. under nitrogen. 10% Potassium hydroxide solution (80 ml.) was then added and heating under reflux was continued for another 3 hr. After addition of sodium chloride solution, washing with ether, and acidification, the liberated oil was isolated with ether. Trituration with pentane gave the trans-*acid* (8·50 g.), m. p. 87—88°. Recrystallisation from hexane gave needles, m. p. 89° (Found: C, 65·5; H, 7·7. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%). A further 0·7 g. of the acid of m. p. 85—87° was obtained on concentration of the mother-liquor.

trans-1-*Hydroxymethyl*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*hexane* (VII; R = CH_2·OH).—The *trans*-acid (10·0 g.) was reduced with lithium aluminium hydride as described for the *cis*-epimer, to give 9·0 g. of the crude *alcohol*. A sample was distilled evaporatively at 180° (bath)/0·01 mm. (Found: C, 68·2; H, 8·4. $C_{16}H_{24}O_4$ requires C, 68·5; H, 8·6%). No crystalline derivatives could be prepared.

The crude alcohol (19·0 g.) was converted into the toluene-*p*-sulphonate, which (28·6 g.) was added to di-*tert.*-butyl sodiomalonate, as described for the *cis*-epimer. The resulting β-[*trans*-2-(2 : 3 : 4-trimethoxyphenyl)*cyclo*hexyl]propionic acid (VII; R = $[CH_2]_2$·CO_2H) crystallised on trituration with pentane, to give 15·64 g. of solid, m. p. 82·5—83° (Gutsche *et al.*[6] give m. p. 82·5—83° for the compound to which they ascribe the *cis*-configuration). Polyphosphoric acid cyclisation of this acid gave *trans*-1 : 2 : 3 : 4 : 4a : 5 : 6 : 11b-octahydro-9 : 10 : 11-trimethoxydibenzo[*a*,*c*]*cyclo*heptatrien-7-one (XIX), needles (from methanol), m. p. 113°. The 2 : 4-dinitrophenylhydrazone had m. p. 247—248°. Gutsche *et al.* report m. p.s 112·5—113·5° and 249—251° for the corresponding "*cis*"-compounds. A mixed m. p. determination, kindly undertaken by Professor C. D. Gutsche, was 112·5—114·5° for the ketone and 247—248·5° for the 2 : 4-dinitrophenylhydrazone.

In the cyclisation of acid (VII; R = $[CH_2]_2$·CO_2H) the best yield of product (XIX) was obtained by adhering closely to the conditions quoted [6] (65—70° for 25 min.); conducting the cyclisation under the conditions found optimal for the *cis*-epimer (see above; 75—85° for 1 hr.) led to a considerable amount of non-polar oils.

cis-1 : 2 : 3 : 4 : 4*a* : 11*b*-*Hexahydro*-9 : 10 : 11-*trimethoxy*-5H-*dibenzo*[a,c]cyclo*heptatriene* (IX).—To the ketone (VIII) (3·50 g.), suspended in methanol (10 ml.) and tetrahydrofuran (10 ml.), sodium borohydride (1 g.) was added at room temperature. After several hours the mixture was warmed on the steam-bath for 10 min. and most of the solvents were then removed *in vacuo*. Water was added and the oily alcohol was isolated with ether. The residue obtained on removal of the solvent was treated in benzene (40 ml.) with naphthalene-β-sulphonic acid (0·10 g.). The solution was refluxed under an azeotropic water-separator for 45 min. The cooled solution was washed, dried, and concentrated. The remaining *product* crystallised immediately on cooling and recrystallised from benzene–methanol as needles, m. p. 98° (2·92 g.) (Found: C, 74·35; H, 8·31. $C_{18}H_{24}O_3$ requires C, 74·97; H, 8·38%), $\lambda_{max.}$ 263 mμ (ε 13,100).

Oxidation of Compound (IX) *by Selenium Dioxide.*—The compound (IX) (7·42 g.) was dissolved in pyridine (28 ml.) and heated to 100°. Selenium dioxide (resublimed; 3·64 g.) was added with stirring in small portions during 4 hr. The mixture was cooled and diluted with ether–benzene, and the precipitated selenium filtered off. The filtrate was washed several times with ice-cold dilute hydrochloric acid, then with water, dilute sodium carbonate solution, and again with water, and dried. The crude product obtained after removal of solvents *in vacuo* (7·85 g.) was chromatographed on activated alumina (Fisher; 140 g.), starting with

hexane–methylene chloride (6 : 1) as solvent and eluant. The first fractions contained unchanged material (*ca.* 0·4 g.); later fractions contained a mixture of the unsaturated ketone (XIII) and substance A (see below) from which A (0·10 g.) was separated by trituration with ether. Methylene chloride and methylene chloride–chloroform (2 : 1) eluted cis-1 : 2 : 3 : 4 : 4*a* : 11*b*-*hexahydro*-9 : 10 : 11-*trimethoxy*-5H-*dibenzo*[a,c]cyclo*heptatrien*-5-*ol* (X) (4·0 g.; m. p. 80—82° after trituration with pentane) mixed with some of substance B (see below) which was not separated at this stage; after several recrystallisations from hexane the alcohol had m. p. 83° (Found: C, 70·9; H, 8·1. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%).

This alcohol (4·0 g.) was shaken with activated manganese dioxide [7] (40 g.) in carbon tetrachloride (40 ml.) for 4 hr. The filtrate and washings therefrom were combined with the ether filtrate from substance A, and the solvents were removed *in vacuo*. The residue was chromatographed on activated alumina (Fisher; 70 g.) starting with hexane as solvent and hexane–methylene chloride as eluant. These solvents eluted cis-1 : 2 : 3 : 4 : 4*a* : 11*b*-*hexahydro*-9 : 10 : 11-*trimethoxy*-5-*oxodibenzo*[a,c]cyclo*heptatriene* (XIII) which, recrystallised from hexane, gave very pale yellow needles (2·75 g.), m. p. 97—99° (Found: C, 71·6; H, 7·5. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·3%), $\lambda_{max.}$ 251, 310 mμ (ε 11,000, 10,000), strong infrared band at 6·09 μ. The 2 : 4-*dinitrophenylhydrazone*, red leaflets from chloroform–ethanol, had m. p. 193° (Found: C, 60·1; H, 5·6; N, 11·7. $C_{24}H_{26}O_7N_4$ requires C, 59·7; H, 5·4; N, 11·6%). On further elution of this chromatogram with chloroform and chloroform–methanol there was obtained, after trituration with ether–hexane, *substance B* [probably (XII)] (0·20 g.), which after recrystallisation from chloroform–*cyclo*hexane formed yellowish needles, m. p. 144° (Found: C, 68·0; H, 7·0; active H, 0·31. $C_{18}H_{22}O_5$ requires C, 67·9; H, 6·95; 1 active H, 0·31%), $\lambda_{max.}$ 251,317 mμ (ε 13,000, 12,000), strong band at 6·06 μ.

Substance A [probably (XI)] on recrystallisation from chloroform–*cyclo*hexane formed stout yellowish needles, m. p. 156° (Found: C, 71·7; H, 8·2. $C_{18}H_{22}O_4$ requires C, 71·5; H, 7·3%), $\lambda_{max.}$ 255, 289 mμ (ε 13,000, 5500), medium infrared band at 6·05 μ. This substance gave no 2 : 4-dinitrophenylhydrazone. On catalytic hydrogenation, with 5% palladium–carbon, 1 mol. of hydrogen was rapidly absorbed. The product was purified by chromatography and recrystallised from methanol to give the ketone (VIII), m. p. and mixed m. p. 107°.

trans-1 : 2 : 3 : 4 : 4*a* : 11*b*-*Hexahydro*-9 : 10 : 11-*trimethoxy*-5H-*dibenzo*[a,c]cyclo*heptatriene* (XX).—The *trans*-ketone (XIX) (5·50 g.) was reduced with sodium borohydride, and the product was dehydrated with naphthalene-β-sulphonic acid in benzene, as described for the *cis*-epimer. The *product* distilled at 160° (bath)/0·01 mm. (4·25 g.) but did not crystallise (Found: C, 75·0; H, 8·3. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·4%), $\lambda_{max.}$ 260 mμ (ε 8950).

On attempted oxidation by selenium dioxide under the conditions described for the *cis*-epimer practically no selenium was precipitated and the starting material was recovered unchanged.

cis-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b*-*Octahydro*-9 : 10 : 11-*trimethoxy*-5-*oxodibenzo*[a,c]cyclo*heptatriene* (XIV).—The unsaturated ketone (XIII) (1·23 g.) was hydrogenated in ethanol (20 ml.) with 5% palladium–calcium carbonate (0·10 g.). Absorption was slow; after about 8 hr. *ca.* 110% of the theoretical amount was taken up. Filtration, evaporation, and crystallisation of the residue from hexane gave the *ketone* (XIV) (0·93 g.), m. p. 113—115°. Further recrystallisation from the same solvent gave needles, m. p. 115·5°, showing the ketone band at 5·90 μ (Found: C, 70·7; H, 8·05. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%). The 2 : 4-*dinitrophenylhydrazone* had m. p. 184—185° (orange-yellow needles from benzene–*cyclo*hexane) (Found: C, 59·7; H, 6·0. $C_{24}H_{28}O_7N_4$ requires C, 59·5; H, 5·8%).

cis-5 : 5-*Ethylenedithio*-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b*-*octahydro*-9 : 10 : 11-*trimethoxydibenzo*[a,c]-cyclo*heptatriene* (XV).—The preceding saturated ketone (0·5 g.), zinc chloride (fused *in vacuo*; 0·6 g.), anhydrous sodium sulphate (0·7 g.), and ethanedithiol (0·5 ml.) were mixed by shaking and left at room temperature for 24 hr. Dilute sodium hydroxide solution and ether–benzene were added; the organic layer was washed repeatedly with water and dried. Removal of solvents left a residue which on trituration with ether–hexane gave the *thioketal* (0·42 g.), m. p. 164—165°. Recrystallisation from benzene–*cyclo*hexane gave needles, m. p. 166° (Found: C, 62·9; H, 7·4. $C_{20}H_{28}O_3S_2$ requires C, 63·1; H, 7·4%).

cis-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b*-*Octahydro*-9 : 10 : 11-*trimethoxydibenzo*[a,c]cyclo*heptatriene* (XVI).—(*a*) Catalytic reduction, in ethanol, of the compound (IX), in presence of 5% palladium–carbon, was very rapid; the theoretical amount of hydrogen was absorbed in 3 min. Filtration and concentration of the filtrate gave the *product*, which crystallised from benzene–methanol in needles, m. p. 102·5—103° (Found: C, 73·92; H, 8·97. $C_{18}H_{26}O_3$ requires C, 74·44; H, 9·03%).

XUM

(*b*) The thioketal (XV) (0·20 g.) was refluxed in ethanol (20 ml.) with Raney nickel catalyst (W 2; teaspoonful) for 5 hr. The mixture was filtered and the residue washed with benzene. The combined filtrate and washings were concentrated in *vacuo* and the residue was taken up in hot hexane. The hexane solution was filtered, the hexane removed, and the residue crystallised from methanol to give product (XVI), m. p. 100—102°, mixed m. p. with the product from (*a*) 102—103°.

trans-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b*-*Octahydro*-9 : 10 : 11-*trimethoxy*-5H-*dibenzo*[a,c]cyclo*heptatriene* (XXI).—This was obtained by catalytic reduction of the compound (XX) as described above for the *cis*-epimer; after distillation at 160° (bath)/0·01 mm. the *product* crystallised (m. p. 72·5—73°) (Found: C, 74·1; H, 9·0%).

trans-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b*-*Octahydro*-9 : 10 : 11-*trimethoxy*-5-*oxodibenzo*[a,c]cyclo*heptatriene* (XVIII).—The *cis*-epimer (XIV) was recovered unchanged after passage in hexane through active basic alumina (Woelm; activity I). It was, however, partially epimerised under the following conditions: (*a*) The ketone (0·3 g.) in ethanol (30 ml.) and 6N-hydrochloric acid (9 ml.) was refluxed for 2½ hr. (*b*) The same compound (0·5 g.) in dry methanol (15 ml.) containing 10% sodium methoxide solution (0·5 ml.) was refluxed for 2 hr. (*c*) The ketone (0·3 g.) in methanol (35 ml.) containing potassium hydroxide (0·4 g.) was refluxed for 45 min.

Quantitative examination of the infrared spectra of the crude products (for estimation method see Zimmerman [4]) obtained by adding sodium chloride solution and ether-extraction showed that in each case between 35 and 45% of the trans-*epimer* had been formed. The latter was obtained pure by fractional crystallisation of the mixture of epimers from hexane; it had m. p. 101·5—102°, and showed the ketone band at 5·87 μ and a band at 7·60 μ not shown by the *cis*-epimer (Found: C, 71·0; H, 8·0. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%). The 2 : 4-*dinitrophenylhydrazone* formed orange-yellow leaflets (from chloroform–ethanol), m. p. 213—214° (Found: C, 59·2; H, 5·7; N, 11·4. $C_{24}H_{28}O_7N_4$ requires C, 59·5; H, 5·8; N, 11·6%).

cis-5-*Acetamido*-1 : 2 : 3 : 4 : 4*a* : 6 : 7 : 11*b*-*octahydro*-9 : 10 : 11-*trimethoxy*-5H-*dibenzo*[a,c]-cyclo*heptatriene* (XVII).—The ketone (XIV) was converted in practically quantitative yield into the *oxime*, by hydroxylamine acetate in aqueous ethanol at pH 7. This formed leaflets, m. p. 215—217° (decomp.) from aqueous dioxan (Found: C, 67·65; H, 7·85. $C_{18}H_{25}O_4N$ requires C, 67·7; H, 7·9%). It (0·8 g.) was reduced by lithium aluminium hydride (0·7 g.) in dry refluxing tetrahydrofuran (20 ml.) for 6 hr. The product obtained after working-up with ice and sodium hydroxide solution, followed by ether-extraction, was treated with acetic anhydride (1 ml.) in pyridine (5 ml.) on the steam-bath for 1 hr. The mixture was treated with ice and extracted with ether. After being washed with dilute hydrochloric acid, water, and sodium carbonate solution the ether layer was dried and the solvent removed. The residue was chromatographed on acid-washed alumina (12 g.) with hexane–methylene chloride as eluant. The crystalline eluates were triturated with ether–hexane, to give the *amide* (0·3 g.), m. p. 143—152°, which exhibited a typical amide infrared spectrum (bands at 6·00 and 2·90 μ). Recrystallisation from *cyclo*hexane gave needles, m. p. 162—178° (Found: N, 4·3. $C_{20}H_{29}O_4N$ requires N, 4·0%). Further recrystallisation from the same solvent failed to improve the m. p. of what was evidently a mixture of 5-epimers.

6 : 6-*Ethylenedioxy*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*heptanecarboxylic Acid* [trans (XXIII) *and* cis (XXII) *Epimers*].—The acid (I; R = CO_2H) (8·90 g.) was reduced with lithium (*ca.* 0·4 g.) in liquid ammonia, as described above for the reduction of the unsaturated acid (V). The residue obtained after removal of ammonia on the steam-bath was dissolved in water; the solution was saturated with sodium chloride, washed with ether, and acidified at 0° under a layer of benzene–ether. The organic layer was thoroughly washed with water, dried, and evaporated *in vacuo*. The remaining oil was dissolved in ether (30 ml.) and the trans-*epimer* was allowed to crystallise at room temperature after seeding, to give 1·0 g. (11%) of material, m. p. 148—150°. Further recrystallisation from benzene–*cyclo*hexane gave prisms, m. p. 152·5—153° (Found: C, 62·4; H, 7·3; OMe 26·5%; equiv., 364. $C_{19}H_{26}O_7$ requires C, 62·3; H, 7·15; OMe, 25·4%; equiv., 366).

The ether filtrate from this *trans*-epimer was concentrated and the remaining oil triturated with hexane. The crude cis-*epimer* slowly separated and was recrystallised from aqueous methanol (in which the *trans*-epimer was much more soluble), to give 6·35 g. (71%) of material, m. p. 126·5—130°. Further recrystallisation from the same solvent gave prisms, m. p. 130—131° (Found: C, 62·0; H, 7·0%; equiv., 363).

The *cis*-epimer (3·0 g.) was treated with diazomethane in ether, and the product refluxed

with sodium methoxide in methanol, then hydrolysed by aqueous alkali, as described for the epimerisation of the saturated acid (VI; R = CO_2H). This gave the *trans*-epimer (2·7 g.), m. p. 148—150°, mixed m. p. 148—151°.

The *trans*-epimer was recovered unchanged after being subjected to the same treatment.

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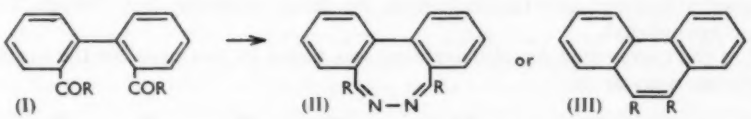
276. *Cyclisations with Hydrazine. Part I. The Preparation of Phenanthrene Compounds and of Pyrene from Aldehydes. A Variation in Reductions of the Wolff–Kishner Type.*

By R. G. R. BACON and W. S. LINDSAY.

Diphenyl-2 : 2′-dialdehyde reacts with hydrazine in polar solvents, at 0° to >100°, and under acidic or alkaline conditions, giving phenanthrene in yields of up to 100%. Phenanthrene may thus be synthesised in four steps from *o*-iodotoluene, and its derivatives may be obtained similarly, *e.g.*, 3 : 6-dinitrophenanthrene from 2-iodo-4-nitrotoluene, through 5 : 5′-dinitrodiphenyl-2 : 2′-dialdehyde. Reaction of hydrazine with 6 : 6′-dimethyldiphenyl-2 : 2′-dialdehyde fails to give 4 : 5-dimethylphenanthrene, but reaction with diphenyl-2 : 2′ : 6 : 6′-tetra-aldehyde gives pyrene. These reductive cyclisations with hydrazine are discussed in relation to known variations in the technique and products of the Wolff–Kishner reaction.

TRICYCLIC compounds are frequently formed by reactions involving 2- and 2′-substituents in a diphenyl derivative, producing a central ring of varying type and size. Recent research [1] on such compounds has been largely concerned with their stereochemistry, some aspects of which are discussed in Part II. An unexplored variation is the formation of cyclic azines (II), containing a central eight-membered (1 : 2-diazocine) ring, a reaction which should occur when 2 : 2′-diacyldiphenyls (I) are treated with hydrazine. As we show in Part II, the expected diazocines were thus obtained from diketones (I; R =



alkyl or aryl). By contrast, the reaction with diphenyl-2 : 2′-dialdehyde (I; R = H) occurred with evolution of nitrogen, and the sole product was phenanthrene (III; R = H). Reductive cyclisation also occurred, though with more difficulty, as an accompaniment to the conversion of the diketones into cyclic azines, giving 9 : 10-disubstituted phenanthrenes (III; R = alkyl or aryl). An example of this dual process was simultaneously observed by Hall, Ladbury, Lesslie, and Turner [2] while studying the reduction of 2 : 2′-diacetyldiphenyl, which is one of the ketones we had examined.

The conversion of diphenyl-2 : 2′-dialdehyde into phenanthrene was studied in some detail, for polar solvents (*e.g.*, ethanol and acetic acid), in the presence of mineral acid or of alkali, and in their absence, at temperatures ranging from below 0° to above 100° (see Table, p. 1379). Approximately 1 mol. of nitrogen was evolved per mol. of phenanthrene produced. Gas evolution was complete in a few minutes at 60° and was faster at this temperature in the presence of alkali. In boiling acetic acid the conversion of the dialdehyde into phenanthrene was quantitative. An alternative method consisted in

[1] See, *e.g.*, *Ann. Reports*, 1953, **50**, 154; Turner and his co-workers, *J.*, 1952, 854, and later papers.
[2] Hall, Ladbury, Lesslie, and Turner, *J.*, 1956, 3475; cf. Bacon and Lindsay, *Chem. and Ind.*, 1956, 1479.

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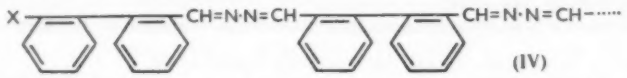
prolonged boiling of an ethanolic solution of 2 : 2′-bisdibromomethyldiphenyl, alkali, and hydrazine, which gave a 60% yield of phenanthrene.



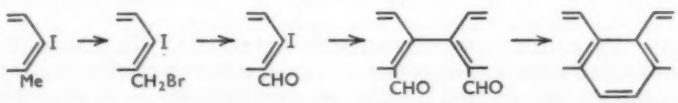
(IV)

When the yield of phenanthrene was not quantitative, the by-products were soluble resins and a yellow polyazine, presumably of type (IV; X = CHO or $CH{:}N{\cdot}NH_2$), which was precipitated during the reaction. The formation of polyazines from dialdehydes or diketones has been reported.[3] In this case it was favoured by low temperature, absence of acid or alkali, and use of aqueous dioxan as the reaction medium. The polyazine can be hydrolysed; a sample obtained by reaction in ethanol at −10° gave phenanthrene in 80% yield when treated with boiling acetic acid.

Reductive cyclisations with hydrazine may prove to be widely applicable to the synthesis of polynuclear compounds through dialdehydes of suitable structure. We therefore examined some methods of obtaining the intermediates. Diphenyl-2 : 2′-dialdehyde was readily prepared in 65% yield from *o*-iodobenzaldehyde and copper at 160°, and reaction was particularly smooth in boiling dimethylformamide.[4] For *o*-iodobenzaldehyde we first used the procedure of Rapson and Shuttleworth,[5] and thus obtained phenanthrene in five steps from *o*-iodobenzoic acid, with an overall yield of 34%. An alternative starting point was *o*-iodotoluene, which with *N*-bromosuccinimide gave *o*-iodobenzyl bromide, convertible into the aldehyde by the Sommelet reaction [6] or through *o*-idobenzyl alcohol, which was oxidised by aqueous persulphate in the presence of silver ion.[7] By the Sommelet reaction, phenanthrene was obtained from *o*-iodotoluene in four steps, with an overall yield of 34%, while the route through the alcohol involved six steps and gave an overall yield of 31%.

Since the persulphate–silver reagent was known to oxidise toluene to benzaldehyde in good yield,[7] corresponding oxidation of *o*-iodotoluene was attempted, but the product was *o*-iodosobenzoic acid. The oxidation of the two adjacent ring substituents may be a co-operative process, since the iodine atom remained unoxidised when *o*-iodobenzoic acid was similarly treated. Another variation unsuccessfully tried was the conversion of 2 : 2′-dimethyldiphenyl into the dialdehyde by direct oxidation and through 2 : 2′-bis-bromomethyldiphenyl.

One of the routes used for phenanthrene was tested in two cases for the synthesis of phenanthrene derivatives:



2-Amino-4-nitrotoluene was converted into 2-iodo-4-nitrotoluene and thence into the hitherto unreported 3 : 6-dinitrophenanthrene; the best overall yield was 13%, in four steps, from the iodide. In this synthesis the least efficient step was the Sommelet reaction; the final reductive cyclisation occurred almost quantitatively in boiling acetic acid and with good yield in boiling ethanol. In the second example, 2-iodo-1 : 3-dimethylbenzene was monobrominated in a methyl group, and then subjected to Sommelet and Ullmann reactions, giving 6 : 6′-dimethyldiphenyl-2 : 2′-dialdehyde in 15% overall yield. The final cyclisation, tried under various conditions, did not give 4 : 5-di-methylphenanthrene, but

[3] Zimmerman and Lochte, *J. Amer. Chem. Soc.*, 1936, **58**, 948; 1938, **60**, 2456; Marvel and Hill, *ibid.*, 1950, **72**, 4819; Naylor and Calico Printers' Association, B.P. 694,451/1953.
[4] Cf. Kornblum and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5782.
[5] Rapson and Shuttleworth, *J.*, 1941, 487.
[6] Angyal, Morris, Rassack, and Waterer, *J.*, 1949, 2704; Angyal, *Org. Reactions*, 1954, **8**, 197.
[7] Bacon, Bott, Doggart, Grime, and Munro, *Chem. and Ind.*, 1953, 897; Bacon and Doggart, unpublished work.

produced polyazine or resins. Treatment of the dialdehyde with excess of anhydrous hydrazine in boiling diethylene glycol, a procedure recommended for the Wolff–Kishner reduction of hindered oxo-steroids,[8] gave some crystalline material which appeared to be 2 : 2′ : 6 : 6′-tetramethyldiphenyl.

Difficulties attending the synthesis of 4 : 5-dimethylphenanthrene are well known [9] and failure to obtain it from the dialdehyde may be attributed to steric factors, associated with the methyl groups in the two other *ortho*-positions. It therefore seemed that if the cyclisation was to be successful with fully *ortho*-substituted diphenyls, the most favourable case should be the 2 : 2′ : 6 : 6′-tetra-aldehyde, which should give pyrene. This tetra-aldehyde has been prepared only by the ozonolysis of pyrene.[10] We repeated this preparation and found that reductive cyclisation with hydrazine in boiling acetic or propionic acid readily reconverted the aldehyde into pyrene, thus reversing the oxidative fission brought about by ozone.

The reductive cyclisations here described may be regarded as a variation in the Wolff–Kishner reaction. Traditional procedures for the normal reduction, $CORR' \longrightarrow CH_2RR'$, involve the use of alkali-metal hydroxide or alkoxide at 180—200°. We found that the disemicarbazone of diphenyl-2 : 2′-dialdehyde underwent normal reduction with potassium hydroxide above 200° to 2 : 2′-dimethyldiphenyl. Several variations on the original Wolff–Kishner methods have been reported. Thus, reductions without alkali, first carried out by Staudinger and Kupfer,[11] appear in about thirty examples in Todd's review.[12] Lock and Stach showed [13] that reduction occurs more readily (with alkali at 80—100°) when applied to the hydrazones of many aromatic aldehydes or ketones. Seibert found [14] a strongly activating effect with α-carbonyl and *o*-nitro-substituents, which permits reduction at about 100°, in the presence or absence of alkali. Various cases of abnormal reduction products are known. A relevant example is the reduction of fluorenone, which gives mainly fluorene or mainly di-9-fluorenyl, depending on conditions.[15] Since di-9-fluorenyl is readily formed by the reduction of difluorenylidene with hydrazine,[15] the "abnormal" course in this reaction may be: $2COR_2 \longrightarrow CR_2{:}CR_2 \longrightarrow CHR_2{\cdot}CHR_2$. Similar reductive couplings, occurring as side-reactions, are the formation of stilbene from benzaldehyde,[16] and of di-(2 : 3-6 : 7-dibenzo-9-fluorenyl) from 2 : 3-6 : 7-dibenzofluorenone.[17]

The reductions now reported are distinguished by their intramolecular and entirely "abnormal" course, by the low temperatures at which they may occur, and by their occurrence in acidic, as well as alkaline solutions. The course taken by the reactions may be due to the proximity of the aldehyde groups, to their conjugation through the diphenyl ring-system, and to the stability to be gained by formation of a new aromatic ring. The literature records a few similar intramolecular reductions, all involving aromatic rings and carbonyl groups in favourable spatial relationship. Thus, tetrabenzo*cyclo*decatetraene-1 : 6-dione gave tetrabenzonaphthalene with hydrazine in alcohol at 130—170°,[18] 5-formylphenanthrene-4-carboxylic acid gave 1-hydroxypyrene with hydrazine in hot acetic acid,[19] and trimethylbrazilone with phenylhydrazine, also in hot acetic acid,[20] gave deoxytrimethylbrazilone, which contains a new olefinic bridge conjugated with benzene rings.

[8] Barton, Ives, and Thomas, *J.*, 1955, 2056.
[9] Newman and Whitehouse, *J. Amer. Chem. Soc.*, 1949, **71**, 3664; Badger, Campbell, Cook, Raphael, and Scott, *J.*, 1950, 2326; Bergmann and Pelchowicz, *J. Amer. Chem. Soc.*, 1953, **75**, 2663; Wittig and Zimmermann, *Chem. Ber.*, 1953, **86**, 629.
[10] Fieser and Novello, *J. Amer. Chem. Soc.*, 1940, **62**, 1855.
[11] Staudinger and Kupfer, *Ber.*, 1911, **44**, 2197.
[12] Todd, *Org. Reactions*, 1948, **4**, 378.
[13] Lock and Stach, *Ber.*, 1943, **76**, 1252; 1944, **77**, 293.
[14] Seibert, *Chem. Ber.*, 1947, **80**, 494; 1948, **81**, 266.
[15] Weisberger and Grantham, *J. Org. Chem.*, 1956, **21**, 1160.
[16] Todd, *J. Amer. Chem. Soc.*, 1949, **71**, 1356.
[17] Cook and Preston, *J.*, 1944, 553.
[18] Suszko and Schillak, *Roczn. Chem.*, 1934, **14**, 1216.
[19] Vollmann, Becker, Corell, and Streeck, *Annalen*, 1937, **531**, 1.
[20] Gilbody and Perkin, *J.*, 1902, 1040; Perkin and Robinson, *J.*, 1908, 489.

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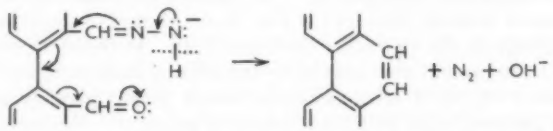
Both ionic and free-radical mechanisms have been proposed for Wolff–Kishner reductions. By adopting the mechanism which Seibert [14] and Szmant *et al.*[21] suggested for conventional Wolff–Kishner reductions, the intramolecular reaction in alkaline solution may be represented as a transformation of the anion of a monohydrazone:



Protonated molecules are presumably involved as intermediates under acidic reaction conditions.

Experimental

Synthesis of Phenanthrene.—o-Iodobenzaldehyde. (*a*) Anthranilic acid gave successively [22, 23] *o*-iodobenzoic acid (83%), *o*-iodobenzoyl chloride (90%), *o*-iodobenzanilide (89%), m. p. 144·5°, and *o*-iodobenzaldehyde (65%), m. p. 37°. The aldehyde was characterised as the *dimedone derivative*, m. p. 139° (decomp.) (Found: C, 55·8; H, 5·5; I, 25·6. $C_{23}H_{27}O_4I$ requires C, 55·8; H, 5·5; I, 25·7%), as the *dimedone anhydride derivative*, m. p. 229° (Found: C, 57·8; H, 5·3; I, 26·7. $C_{23}H_{25}O_3I$ requires C, 58·0; H, 5·3; I, 26·7%), and as the *azine*, which crystallised from ethanol in yellow needles, m. p. 182° (Found: C, 36·7; H, 2·2; I, 5·9. $C_{14}H_{10}N_2I_2$ requires C, 36·5; H, 2·2; I, 6·1%).

(*b*) *o*-Iodotoluene (0·5 mole) was heated for 3 hr. in boiling carbon tetrachloride with pure dry *N*-bromosuccinimide [23] (0·2—0·3 mole) and benzoyl peroxide (0·01 mole), giving *o*-iodobenzyl bromide, m. p. 55·5°, in a yield of 70—80% after allowance for *o*-iodotoluene recovered by distillation. *o*-Iodotoluene could not be converted into *o*-iodobenzyl chloride with sulphuryl chloride.[24] With excess of anhydrous sodium acetate in refluxing acetic acid, *o*-iodobenzyl bromide gave *o-iodobenzyl acetate* (80%), b. p. 92°/0·4 mm., n_D^{25} 1·5788 (Found: C, 39·2; H, 3·3. $C_9H_9O_2I$ requires C, 39·1; H, 3·3%). With boiling aqueous potassium hydroxide the acetate gave *o*-iodobenzyl alcohol (92%), which crystallised from benzene or light petroleum in needles, m. p. 91°; Olivier [25] records m. p. 89·5—90°. The alcohol was characterised as the *phenylurethane*, m. p. 103° (Found: C, 47·7; H, 3·6; N, 3·8. $C_{14}H_{12}O_2NI$ requires C, 47·6; H, 3·4; N, 4·0%), and as the *α-naphthylurethane*, m. p. 152° (Found: C, 53·8; H, 3·7; N, 3·2. $C_{18}H_{14}O_2NI$ requires C, 53·6; H, 3·5; N, 3·5%). The alcohol (0·02—0·2 mole) was oxidised to *o*-iodobenzaldehyde, in 60—80% yield, by 3 hours' stirring at 60° with aqueous 0·2M-sodium persulphate (1 mol.), containing silver nitrate (0·01—0·04 mol.).[7] The aldehyde was purified by steam-distillation.

(*c*) *o*-Iodobenzyl bromide was prepared, as in method (*b*), by using *N*-bromosuccinimide (0·3 mole), and the crude crystalline product was mixed with a slight excess of hexamethylenetetramine in chloroform at room temperature. Next day, the precipitated hexamethylenetetramine salt was collected in 76% yield (calc. on *N*-bromosuccinimide) and was converted into *o*-iodobenzaldehyde (68% yield) by the procedure of Angyal *et al.*[6]

(*d*) *o*-Iodotoluene failed to give *o*-iodobenzaldehyde when oxidised by aqueous sodium persulphate (2 mol.), containing silver nitrate, but gave some *o*-iodosobenzoic acid, which was obtained in 80% yield (after allowance for recovered *o*-iodotoluene) by using 4 mol. of persulphate; *o*-iodotoluene (22 g.) was stirred for 3 hr. at 60° with a solution of sodium persulphate (96 g.) in 0·007M-aqueous silver nitrate (300 ml.), giving unchanged *o*-iodotoluene (10 g.) and *o*-iodosobenzoic acid (12 g.), m. p. 222—222·5° (Found: C, 31·9; H, 2·0; I, 47·9. Calc. for $C_7H_5O_3I$: C, 31·8; H, 1·9; I, 48·1%). Fichter records decomposition at 223—225°.[26] *o*-Iodobenzoic acid gave no *o*-iodosobenzoic acid when similarly treated with sodium persulphate (1 mol.) in aqueous silver nitrate.

[21] Szmant, Harnsberger, Butler, and Barie, *J. Amer. Chem. Soc.*, 1952, **74**, 2724.
[22] Cohen and Raper, *J.*, 1904, 1271.
[23] Chapman and Williams, *J.*, 1952, 5044.
[24] Kharasch and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 2142.
[25] Olivier, *Rec. Trav. chim.*, 1923, **42**, 516.
[26] Fichter, *Helv. Chim. Acta*, 1925, **8**, 438.

Diphenyl-2 : 2′-dialdehyde.—(*a*) *o*-Iodobenzaldehyde (23 g.) was stirred with copper bronze (20 g.) in refluxing dimethylformamide (30 ml.) for 3 hr. The product was extracted with chloroform and the extract distilled, to give diphenyl-2 : 2′-dialdehyde (65%), b. p. 169°/2·5 mm., pale yellow crystals, m. p. 62°. Similar yields of dialdehyde were obtained at 160° in the absence of dimethylformamide, but much more resin was then produced (cf. Rapson and Shuttleworth [5]). The derived *tetra-acetate* crystallised from ethanol in pale yellow needles, m. p. 133° (Found: C, 63·6; H, 5·15. $C_{22}H_{22}O_8$ requires C, 63·8; H, 5·35%). The *disemicarbazone* had m. p. 230° (Found: C, 59·3; H, 5·1; N, 25·8. $C_{16}H_{16}O_2N_6$ requires C, 59·3; H, 5·0; N, 25·9%). The oxime had m. p. 177°; Mayer [27] gives 175—176°.

(*b*) 2 : 2′-Bisbromomethyldiphenyl, m. p. 91°, was prepared in 65—95% yield from 2 : 2′-dimethyldiphenyl (1 mol.), *N*-bromosuccinimide (2·1 mol.), and benzoyl peroxide (0·1 mol.) in boiling carbon tetrachloride.[28] The dibromide and hexamethylenetetramine gave a salt of indefinite composition, from which no dialdehyde could be obtained. Treatment of the dibromide with sodium acetate in acetic acid gave 2 : 2′-bisacetoxymethyldiphenyl (69%), b. p. 207°/10 mm., converted by aqueous potassium hydroxide into 2 : 2′-bishydroxymethyldiphenyl (96%), m. p. 112°.[28, 29] Oxidation of this alcohol with aqueous sodium persulphate containing silver nitrate yielded only resin.

Phenanthrene.—A solution of diphenyl-2 : 2′-dialdehyde (2·00 g., 0·0095 mole) in acetic acid (100 ml.) was heated under reflux while a solution of 60% hydrazine hydrate (1·0 g., 0·012 mole) in acetic acid (20 ml.) was added dropwise during 1 hr. Refluxing was continued for 2 hr. more, the solvent then removed under reduced pressure, and the residue taken up in benzene. Chromatography of the solution on a column of alumina yielded pure phenanthrene (1·61 g., 95%) as colourless plates, m. p. and mixed m. p. 99·5° (Found: C, 94·4; H, 5·6. Calc. for $C_{14}H_{10}$: C, 94·4; H, 5·6%). It was characterised as the picrate, m. p. and mixed m. p. 143°.

Other preparations of phenanthrene, made from the dialdehyde and hydrazine under varied conditions, are summarised in the Table. Normally, 1·00 or 0·50 g. of dialdehyde was used, in 50 ml. of solvent. In some experiments the evolved nitrogen was measured in a gas burette. In ethanol at 60° gas evolution was complete in about 20 min. and if potassium hydroxide was also present it was too fast for measurement unless the hydrazine was added dropwise. Yellow polyazine was precipitated under some conditions. The only other by-products were soluble resins, which could be eluted only partially from an alumina column. In no case was unchanged dialdehyde recovered.

In the preparation summarised in the first line of the Table, the ethanol solution was kept for 2 days in a refrigerator, the hydrazine being added in two lots. Polyazine precipitation

Temp.	Reaction medium	N_2H_4 : dialdehyde (mol.)	N_2 (mol.) evolved per mol. of dialdehyde	Polyazine (wt. % of dialdehyde used)	Phenanthrene yield (%)	Notes
−10°	EtOH	2 : 1	—	30, 28	19, 15	*a*
60	EtOH	1 : 1	0·49	26	53	
60	EtOH	2·5 : 1	0·47	0	38	*c*
78	EtOH	2·5 : 1	—	0	90	
60	EtOH–H_2O (1 : 1 v/v)	1 : 1	0·52	15	48	
78	" "	5 : 1	—	0	49	*b*
60	EtOH + KOH (~1 mol.)	1 : 1	—, 0·31	0	49, 44	
60	" "	2·5 : 1	0·63, 0·63	0	66, 78	*c*
78	EtOH–10N-aq. H_2SO_4 (4 : 1 v/v)	1·1 : 1	—	0	94	*b*
60	Pr^iOH	1 : 1	0·43	16	40	
60	Dioxan–H_2O (1 : 1 v/v)	1 : 1	0·11	80	10	
80	EtOH–AcOH (3 : 1 v/v)	2·5 : 1	—	0	97	
117	AcOH	2·5 : 1	—	0	99	*c*

(*a*) Cf. text. (*b*) Hydrazine sulphate used. (*c*) Hydrazine added dropwise.

then appeared to be complete. Analyses of the polymer corresponded, *e.g.*, with a trimer or tetramer (*M*, 600—800) with one terminal hydrazone group and one terminal aldehyde group (Found: C, 79·0, 79·4; H, 5·4, 5·1; N, 13·6, 13·6. Calc. for trimer, $C_{42}H_{32}ON_6$: C, 79·2; H, 5·0; N, 13·2; for tetramer, $C_{56}H_{42}ON_8$: C, 79·8; H, 5·0; N, 13·3%). This polyazine gradually

[27] Mayer, *Ber.*, 1911, **44**, 2298.
[28] Wenner, *J. Org. Chem.*, 1952, **17**, 523; cf. ref. 29.
[29] Hall, Lesslie, and Turner, *J.*, 1950, 711.

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dissolved in boiling acetic acid, with evolution of nitrogen, giving a red solution, from which phenanthrene was obtained (80% yield on polyazine) by evaporation and chromatography. When polyazine had been separated from the original reaction mixture, ethanol was removed from the filtrate at 20° in a vacuum and the residue chromatographed with benzene on alumina, phenanthrene (15—20%) and resin being obtained. If the ethanolic filtrate was refluxed for 2 hr. before evaporation and chromatography, the yield of phenanthrene was 60%.

Phenanthrene from 2 : 2′-*bisdibromomethyldiphenyl.* The tetrabromide [30] was recovered unchanged after 2 days in boiling ethanol containing excess of hydrazine. When the tetrabromide (1·00 g., 0·002 mole) was heated for 5 days with hydrazine hydrate (0·008—0·016 mole) and potassium hydroxide (0·008 mole) in boiling aqueous (1 : 1) ethanol (150 ml.), chromatography of the product on alumina yielded phenanthrene (60%) and unchanged tetrabromide (30%).

Wolff–Kishner Reduction of Diphenyl-2 : 2′-*dialdehyde Disemicarbazone.*—The semicarbazone (2·0 g.) was heated for 3 hr. at 230° with potassium hydroxide (0·5 g.) and the product diluted with water, ether-extracted, and chromatographed in benzene on alumina, to yield 2 : 2′-dimethyldiphenyl (0·70 g., 62%), m. p. and mixed m. p. 16—17°.

Synthesis of 3 : 6-*Dinitrophenanthrene.*—2-*Iodo*-4-*nitrobenzaldehyde.* 2-Amino-4-nitrotoluene, m. p. 100—102° (acetyl derivative, m. p. 152°), was converted through the diazonium salt into 2-iodo-4-nitrotoluene (63% on 0·4 mole scale), b. p. 114—116°/0·2 mm., yellow needles, m. p. 54° (from ethanol); Willgerodt and Kok [31] and Wheeler [32] give m. p. 58° (Found: C, 32·2; H, 2·0; N, 5·05. Calc. for $C_7H_4O_2NI$: C, 31·9; H, 2·3; N, 5·3%). This compound (0·2 mole) was treated in boiling carbon tetrachloride (50 ml.) for 7 hr. with *N*-bromosuccinimide (0·2 mole) and benzoyl peroxide (3 g.), yielding 2-*iodo*-4-*nitrobenzyl bromide* (42 g., 67%), as pale yellow needles, m. p. 84° after recrystallisation from light petroleum (Found: C, 24·8; H, 1·4; N, 3·9. $C_7H_5O_2NBrI$ requires C, 24·6; H, 1·5; N, 4·1%). Reaction of the bromide with hexamethylenetetramine in boiling chloroform resulted in 97% conversion into the *salt*, m. p. 184—185° (decomp.) (Found: C, 32·6; H, 3·7; N, 15·1. $C_{13}H_{17}O_2N_5BrI$ requires C, 32·4; H, 3·5; N, 14·6%). This salt (30 g.) was heated under reflux for 1·5 hr. with 60% aqueous acetic acid (180 ml.) and the product added to 3N-hydrochloric acid (250 ml.) to yield 2-*iodo*-4-*nitrobenzaldehyde* (5·6 g., 32%), which crystallised from *cyclo*hexane in pale yellow needles, m. p. 84·5° (Found: C, 30·3; H, 1·7; N, 4·9. $C_7H_4O_3NI$ requires C, 30·3; H, 1·5; N, 5·1%). It was characterised as the *oxime*, m. p. 134° (Found: C, 28·5; H, 1·8; N, 9·6. $C_7H_5O_3N_2I$ requires C, 28·8; H, 1·7; N, 9·6%), and as the *dimedone derivative*, m. p. 212° (decomp.) (Found: C, 51·2; H, 4·7; N, 2·5. $C_{23}H_{26}O_6NI$ requires C, 51·2; H, 4·8; N, 2·6%).

5 : 5′-*Dinitrodiphenyl*-2 : 2′-*dialdehyde.* 2-Iodo-4-nitrobenzaldehyde (6·0 g.) and copper bronze (4 g.) were heated for 2 hr. under nitrogen in refluxing dimethylformamide (30 ml.). Extraction with chloroform and removal of solvents left a solid product, from which *p*-nitrobenzaldehyde (0·4 g., 12%), m. p. 105—105·5°, was removed with *cyclo*hexane. Recrystallisation of the residue from aqueous acetic acid gave 5 : 5′-*dinitrodiphenyl*-2 : 2′-*dialdehyde* (2·1 g., 65%) in pale yellow plates, m. p. 203·5° (Found: C, 56·2; H, 2·6; N, 9·5. $C_{14}H_8O_6N_2$ requires C, 56·0; H, 2·7; N, 9·35%).

3 : 6-*Dinitrophenanthrene.* 100% Hydrazine hydrate (0·15 g., 0·003 mole) in glacial acetic acid (5 ml.) was added during 1 hr. to the aldehyde (0·50 g., 0·0017 mole) in refluxing glacial acetic acid and refluxing was continued for 4 hr. longer. 3 : 6-*Dinitrophenanthrene* was obtained in 80—96% yield as a precipitate, m. p. 278—279°. Recrystallisation from acetic acid gave yellow needles, m. p. 282—282·5° (Found: C, 62·7; H, 3·0; N, 10·8. $C_{14}H_8O_4N_2$ requires C, 62·6; H, 3·0; N, 10·5%). Reaction for 2 hr. in boiling ethanol gave a yield of 72%. The 3 : 6-dinitrophenanthrene was almost insoluble in benzene, did not fluoresce in ultraviolet light, and was unchanged when treated with peracetic acid under conditions [33] which resulted in a 57% yield of diphenyl-2 : 2′-dicarboxylic acid from phenanthrene.

Attempted Synthesis of 4 : 5-*Dimethylphenanthrene.*—2-*Iodo*-3-*methylbenzyl bromide.* 2-Iodo-1 : 3-dimethylbenzene was obtained in 62% yield from 2-amino-1 : 3-dimethylbenzene.[34] When 50 g. (0·21 mole) were heated for 5 hr. with *N*-bromosuccinimide (38 g., 0·21 mole) and benzoyl

[30] Kenner and E. G. Turner, *J.*, 1911, 2101.
[31] Willgerodt and Kok, *Ber.*, 1908, **41**, 2077.
[32] Wheeler, *Amer. Chem. J.*, 1910, **44**, 139.
[33] Karrman and Laakso, *Acta Chem. Scand.*, 1947, **1**, 449.
[34] Jacobs, Reed, and Pacovska, *J. Amer. Chem. Soc.*, 1951, **73**, 4505.

peroxide (2 g.) in boiling carbon tetrachloride, 35 g. were recovered unchanged and the product was 2-iodo-3-methylbenzyl bromide (12·2 g., 61% after allowance for the recovered iodide), b. p. 144°/1·5 mm. The bromide was characterised as the yellow *thiuronium picrate* (92% yield in boiling ethanol), m. p. 223° (decomp.) (Found: C, 34·2; H, 2·7; N, 12·5. $C_{15}H_{14}O_7N_5SI$ requires C, 33·7; H, 2·6; N, 13·1%), and as the nearly colourless *hexamethylenetetramine salt* (92% yield in boiling chloroform), m. p. 180—183° (decomp.) (Found: C, 36·7; H, 4·5; N, 12·4. $C_{14}H_{20}N_4BrI$ requires C, 37·3; H, 4·5; N, 12·4%). With sodium acetate in boiling acetic acid the bromide gave *2-iodo-3-methylbenzyl acetate* (77%), b. p. 108°/0·6 mm., n_D^{25} 1·5808 (Found: C, 41·6; H, 3·6. $C_{10}H_{11}O_2I$ requires C, 41·4; H, 3·8%). The acetate in boiling aqueous potassium hydroxide gave *2-iodo-3-methylbenzyl alcohol* (92%), m. p. 70° on recrystallisation from light petroleum (Found: C, 39·0; H, 3·8; I, 51·3. C_8H_9OI requires C, 38·7; H, 3·6; I, 51·2%), characterised as the *phenylurethane*, m. p. 119° (Found: C, 48·9; H, 3·9; N, 4·0. $C_{15}H_{14}O_2NI$ requires C, 49·1; H, 3·8; N, 3·8%).

2-Iodo-3-methylbenzaldehyde. The above hexamethylenetetramine salt (90 g., 0·2 mole) was heated for 2 hr. in refluxing 50% aqueous acetic acid (180 ml.) and the product was treated with an equal volume of 3N-hydrochloric acid, the aldehyde separating (27 g., 55%) and being obtained in almost colourless needles, m. p. 53—54°, on recrystallisation from hexane; Mayer [35] gives m. p. 55—56°. It was characterised as the *semicarbazone*, m. p. 224° (Found: C, 35·8; H, 3·3; N, 13·9. $C_9H_{10}ON_3I$ requires C, 35·7; H, 3·3; N, 13·9%), as the *dimedone derivative*, m. p. 197° (decomp.) (Found: C, 56·8; H, 6·0. $C_{24}H_{29}O_4I$ requires C, 56·7; H, 5·7%), and as the *dimedone anhydride derivative*, m. p. 247° (Found: C, 58·7; H, 5·5. $C_{24}H_{27}O_3I$ requires C, 58·7; H, 5·5%).

6 : 6′-Dimethyldiphenyl-2 : 2′-dialdehyde. 2-Iodo-3-methylbenzaldehyde (20 g., 0·08 mole) was heated for 3 hr. at 190—220° with an equal weight of copper bronze. Ether-extraction and distillation of the residue at reduced pressure yielded a little *m*-tolualdehyde (semicarbazone, m. p. 217°) and 6 : 6′-dimethyldiphenyl-2 : 2′-dialdehyde (4·8 g., 50%), m. p. 114° (from aqueous methanol) (Found: C, 80·7; H, 6·1. Calc. for $C_{16}H_{14}O_2$: C, 80·7; H, 5·9%); Mayer [35] gives m. p. 118°. It formed a *disemicarbazone*, m. p. 254—256° (Found: C, 61·1; H, 6·2; N, 23·6. $C_{18}H_{20}O_2N_6$ requires C, 61·4; H, 5·7; N, 23·8%).

Treatment of the Dialdehyde with Hydrazine.—In boiling ethanol or boiling diethylene glycol the only product was a precipitate of polyazine (~85% of the weight of dialdehyde). In boiling ethanol containing potassium hydroxide, or in boiling acetic, propionic, or chloroacetic acid, no polyazine appeared, but chromatography of the products yielded only gums. After treatment with a large excess of anhydrous hydrazine in boiling dry diethylene glycol,[8] chromatography gave a crystalline fraction (~45%) which was not 4 : 5-dimethylphenanthrene. Recrystallisation from methanol gave colourless plates, m. p. 65—67·5°; Carlin [36] records m. p. 66—67° for 2 : 2′ : 6 : 6′-tetramethyldiphenyl. The ultraviolet absorption spectrum ($\lambda_{max.}$ 262 mμ, log ε 271) was similar to that reported for 2 : 2′ : 4 : 4′ : 6 : 6′-hexamethyldiphenyl.[37]

Opening and Re-formation of the Pyrene Ring System.—Diphenyl-2 : 2′ : 6 : 6′-tetra-aldehyde. Ozonolysis of pyrene, followed by hydrogenation, as described by Fieser and Novello [10] gave a product which was purified by chromatography in ethyl acetate on alumina, or by recrystallisation from water or benzene–hexane. The yield was similar (12% from 3 g. of pyrene), but the m. p. was 155·5°; Fieser and Novello give 162—162·8° (Found: C, 71·8; H, 4·0. Calc. for $C_{16}H_{10}O_4$: C, 72·2; H, 3·8%).

Pyrene. The tetra-aldehyde (250 mg.) in boiling acetic or propionic acid (45 ml.) was treated with excess of 100% hydrazine hydrate (500 mg.) in 5 ml. of the same solvent, added dropwise during 1—2 hr. A yellow precipitate, probably polyazine, was formed, but disappeared during 10 hours' further refluxing. Removal of solvent, followed by chromatography in benzene on alumina, yielded pure pyrene (63—66%), m. p. and mixed m. p. 149°. It was converted into the picrate, m. p. and mixed m. p. 226—227° (Found: C, 60·9; H, 2·6; N, 9·3. Calc. for $C_{22}H_{13}O_7N_3$: C, 61·3; H, 3·0; N, 9·7%).

We thank the Chemical Society for a grant from the Research Fund.

THE QUEEN'S UNIVERSITY, BELFAST. [*Received, November 14th*, 1957.]

[35] Mayer, *Ber.*, 1914, **47**, 406.
[36] Carlin, *J. Amer. Chem. Soc.*, 1945, **67**, 928.
[37] O'Shaughnessy and Rodebush, *ibid.*, 1940, **62**, 2906.

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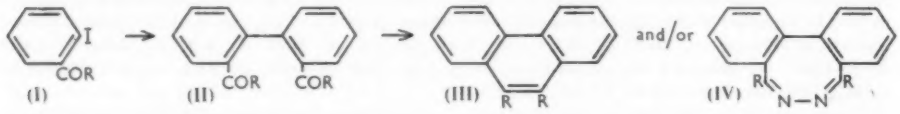
277. *Cyclisations with Hydrazine. Part II.* Conversion of* 2 : 2′-*Diacyldiphenyls into Compounds of the Phenanthrene and* 4 : 5-6 : 7-*Dibenzo*-1 : 2-*diazocine Series.*

By R. G. R. Bacon and W. S. Lindsay.

2 : 2′-Diacyldiphenyls are converted by hydrazine into phenanthrenes or 4 : 5-6 : 7-dibenzo-1 : 2-diazocines containing alkyl (or aryl) substituents in the 9 : 10- and 3 : 8-positions respectively. The influence of reaction conditions on the nature of the product is reported for the cyclisation of diacetyl-, dipropionyl-, and dibenzoyl-diphenyl. The stability of the dibenzodiazocines indicates that in general they are unlikely to be intermediates in the formation of the phenanthrenes. The ultraviolet and infrared absorption spectra of the dibenzodiazocines are discussed and compared with those of open-chain azines, Ar·CR:N·N:CRAr.

In Part I and in an earlier note [1] we referred to differences between diketones of type (II) and the corresponding aldehydes (R = H) in their reactions with hydrazine. In cases which we have so far examined, both classes of compound undergo reductive cyclisations to phenanthrenes (III), but only the diketones also yield 3 : 8-dialkyl(or -diaryl)-4 : 5-6 : 7-dibenzo-1 : 2-diazocines (IV). We now report details of these reactions for three diketones (R = Me, Et, and Ph) and describe some properties of the resulting diazocines.



Diketones (II), also obtainable from phenanthraquinone,[2,3] were prepared in 60—75% yield by an Ullmann reaction on *o*-iodophenyl ketones (I), derived from *o*-iodobenzoyl chloride. The latter gave *o*-iodobenzophenone by a Friedel–Crafts reaction [4] and gave *o*-iodoacetophenone, in high yield, on treatment with diethyl ethoxymagnesiomalonate. This reagent, used in similar cases by Walker and Hauser [5] and by Bowman,[6] proved superior to ethyl sodioacetoacetate.[7,8] The homologous *o*-iodopropiophenone was obtained similarly from diethyl ethoxymagnesiomethylmalonate. Under appropriate conditions, described below, yields of up to 70% were obtained in the conversion of the diketones into the diazocines (IV), which may thus be synthesised from *o*-iodobenzoyl chloride in three steps and with overall yields of up to 40%. Only in one experiment (Table 3) was a high yield of a phenanthrene (III) obtained; yields were more commonly 20—30%.

Cyclisation of 2 : 2′-diacetyldiphenyl with hydrazine occurred readily in polar solvents (Table 1). The best yields of the diazocine were obtained at 0°, but even so a little reductive cyclisation to 9 : 10-dimethylphenanthrene occurred. Moderate yields of the hydrocarbon were obtained at ~80—180°, but diazocine formation was a strongly competitive reaction under nearly all conditions. Both reactions occurred in acidic media but, in contrast to the case of diphenyl-2 : 2′-dialdehydes (Part I), only resins were

* Part I, preceding paper.

[1] Bacon and Lindsay, *Chem. and Ind.*, 1956, 1479.
[2] Zincke and Tropp, *Annalen*, 1908, **363**, 302.
[3] Hall, Ladbury, Lesslie, and Turner, *J.*, 1956, 3475.
[4] Wachter, *Ber.*, 1893, **26**, 1744.
[5] Walker and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386.
[6] Bowman, *J.*, 1950, 322.
[7] Thorp and Brunskill, *J. Amer. Chem. Soc.*, 1915, **37**, 1258.
[8] Rapson and Shuttleworth, *J.*, 1941, 487.

formed under alkaline conditions. The sensitivity of 2 : 2′-diacetyldiphenyl towards alkali was noted by Turner and his co-workers during their study [3] of the anomalous behaviour of this diketone with various reducing agents. They too observed the dual reaction with hydrazine in warm ethanol, obtaining the diazocine and 9 : 10-dimethylphenanthrene in yields of 53% and ~4% respectively.

From 2 : 2′-dipropionyldiphenyl and hydrazine in ethanol or carboxylic acids, 3 : 8-diethyl-4 : 5-6 : 7-dibenzo-1 : 2-diazocine was obtained exclusively, the best yield being at the lowest temperature (Table 2). 9 : 10-Diethylphenanthrene was obtained, together with the diazocine, by using excess of anhydrous hydrazine in diethylene glycol, a technique recommended for Wolff–Kishner reductions of hindered ketones.[9]

2 : 2′-Dibenzoyldiphenyl proved much more resistant to hydrazine (Table 3). In ethanol, or preferably in acetic acid, reduction could be achieved in pressure vessels at 200—280°, the product being 9 : 10-diphenylphenanthrene exclusively. The hydrocarbon was obtained more conveniently, and in high yield, by using excess of anhydrous hydrazine in hot diethylene glycol at atmospheric pressure. When hydrazine hydrate was employed in this medium the main product was 3 : 8-diphenyl-4 : 5-6 : 7-dibenzo-1 : 2-diazocine. Other instances are known in which reduction by anhydrous hydrazine gives a different product from reduction by the hydrate. For example, Dutt and Sen obtained phenanthrone from phenanthraquinone with anhydrous hydrazine, but obtained 9 : 10-dihydroxyphenanthrene with the hydrate.[10]

It might be supposed that the phenanthrenes arise by loss of nitrogen from the diazocines, just as stilbenes are formed from aromatic aldazines, Ar·CH:N·N:CHAr. However, aldazine decompositions require a relatively high temperature (280—300°),[11] and yields are poor. For aromatic ketazines, Ar·CR:N·N:CRAr, it is reported that even higher temperatures (300—350°) are required for decomposition and that stilbenes are not produced.[12] Dimethyl- and diethyl-diazocines had considerable stability. They yielded no phenanthrenes in the molten state above 300° or on prolonged boiling in acetic acid. The dimethyl- but not the diethyl-compound gave a trace of the phenanthrene in boiling diethylene glycol. In the presence of excess of hydrazine there was very slow conversion of diazocines into phenanthrenes (10—20% in 24 hr.) in boiling diethylene glycol or acetic acid. Comparison of such data (see Experimental section) with those in Tables 1, 2, and 3 suggests that the diazocines do not contribute as intermediates to an important degree, except, probably, with excess of hydrazine present at the higher temperatures. Turner and his co-workers concluded that 9 : 10-dimethylphenanthrene was unlikely to have been formed *via* the diazocine under their conditions. Similar comparative experiments were not possible when conversions of diphenyldialdehydes were studied (Part I), since no conditions have yet been discovered for obtaining the related diazocines.

Construction of three-dimensional (" Catalin "-type) molecular models for the 1 : 2-diazocines showed that formation of the central ring necessitates *cis*-linkages (in relation to the rings of the diphenyl system) at both ·CR:N· bonds, as shown in Fig. 1. The diazocines are diaza*cyclo*octatetraenes and the " tub " form possessed by the eight-membered ring in this model is similar to that preferred by Pitzer and his co-workers for *cyclo*octatetraene itself.[13] The twist in the chain of four bridge atoms fixes the benzene rings at an inclination to each other of ~67° and the model can be constructed in enantiomorphous forms. The resolution of 4 : 5-6 : 7-dibenzo-1 : 2-diazocine derivatives has yet to be attempted; a derivative of the isomeric 5 : 6-7 : 8-dibenzo-1 : 4-diazocine system has already been resolved.[14]

A related carbocyclic compound, 1 : 2-3 : 4-dibenzo*cyclo*octatetraene, could not be

[9] Barton, Ives, and Thomas, *J.*, 1955, 2056.
[10] Dutt and Sen, *J.*, 1923, 3420; Dutt, *J.*, 1925, 2971.
[11] Cf., *e.g.*, Pascal and Normand, *Bull. Soc. chim. France*, 1911, **9**, 1029, 1059; 1912, **11**, 21.
[12] Howard and Hilbert, *J. Amer. Chem. Soc.*, 1932, **54**, 3628.
[13] Person, Pimentel, and Pitzer, *ibid.*, 1952, **74**, 3437.
[14] Bell, *J.*, 1952, 1527.

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obtained by Rapson and Shuttleworth [8] by treating 1 : 4-di-*o*-iodophenylbuta-1 : 3-diene with copper; cyclisation would presumably by assisted by a *cis-cis*-diene structure. We likewise failed to convert *o*-iodoacetophenone azine (V) into the diazocine (IV; R = Me), but we did obtain some 9 : 10-dimethylphenanthrene in a reaction involving both an Ullmann condensation and loss of nitrogen:

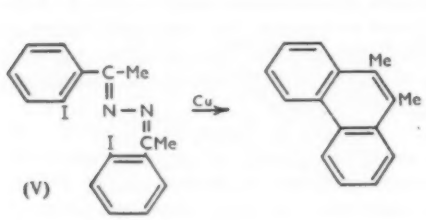
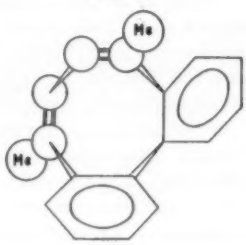


FIG. 1.



We have also examined some spectroscopic properties of the diazocines. In the near-ultraviolet region the effects of 2 : 2′-bridges on the characteristic diphenyl peak (249 mμ) have previously been studied for more than thirty tricyclic compounds,[15] but in few of these cases does the bridge contain more than three linking atoms. A saturated chain of four

FIG. 2. FIG. 3.

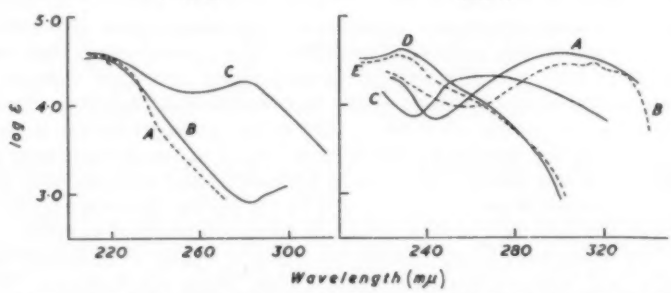


FIG. 2. *Spectra of*: (*A*) 3 : 8-*dimethyl*-4 : 5-6 : 7-*dibenzo*-1 : 2-*diazocine*, (*B*) 3 : 8-*diethyl*-4 : 5-6 : 7-*dibenzo*-1 : 2-*diazocine*, (*C*) 3 : 8-*diphenyl*-4 : 5-6 : 7-*dibenzo*-1 : 2-*diazocine*.

FIG. 3. *Spectra of*: (*A*) *benzaldehyde azine*, (*B*) o-*iodobenzaldehyde azine*, (*C*) *acetophenone azine*, (*D*) o-*iodoacetophenone azine*, (*E*) o-*iodopropiophenone azine*.

carbon atoms causes a displacement of the peak to shorter wavelengths and a reduction in intensity, indicating reduced conjugation in the benzene rings, which are thought to be inclined at 60—80° to each other.[16] On the other hand, in *apo*galanthamine,[17] containing the bridge $CH_2{\cdot}CH_2{\cdot}NMe{\cdot}CH_2$, and in phenyl(or methyl)dihydrothebaine,[18] containing the bridge $CH_2{\cdot}CHR{\cdot}NMe{\cdot}CH_2{\cdot}CH_2$, a band of reduced intensity appears at longer wavelengths.* The ultraviolet absorption spectrum for Turner's 3 : 8-dimethyl-4 : 5-6 : 7-dibenzo-1 : 2-diazocine [3] was recently recorded by Beaven and Johnson.[19] Our own spectra for this and for the diethyl- and diphenyl-compounds are shown in Fig. 2. The spectra of

* Comparison is complicated in these cases because an *o*-hydroxyl group is also present.

[15] Beaven, Turner, and their co-workers, *J.*, 1952, 854, and later papers; Braude and Waight in Klyne's "Progress in Stereochemistry," Vol. I, Butterworths, London, 1954; Truce and Emrick, *J. Amer. Chem. Soc.*, 1956, **78**, 6130 (earlier data are there collected).

[16] Beaven, Bird, Hall, Johnson, Ladbury, Lesslie, and Turner, *J.*, 1955, 2708.

[17] Kobayashi and Uyeo, *J.*, 1957, 638.

[18] Small, Sargent, and Bralley, *J. Org. Chem.*, 1947, **12**, 839; cf. Bentley and Robinson, *J.*, 1952, 947.

[19] Beaven and Johnson, *J.*, 1957, 651.

the two dialkyl derivatives, with peaks (~215 mμ) at much shorter wavelength than diphenyl, are similar to those of 2 : 2′-linked diphenyl derivatives containing the bridge CH_2·AsR·CH_2, in which the estimated deviation [20] of the benzene rings from coplanarity is ~63°.

Comparison may also be made with the absorption spectra of open-chain azines, Ar·CR:N·N:CRAr (R = H, alkyl, or aryl). We were led to examine some spectra in this series (Fig. 3) on observing the absence of the usual yellow colour in some available *o*-iodo-substituted azines. Other investigators have considered both steric and polar factors in interpreting the spectroscopic characteristics of series of nuclear-substituted aromatic

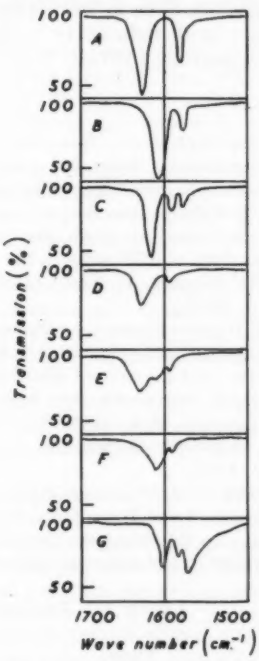


FIG. 4.

Spectra of:

(*A*) *Benzaldehyde azine.*
(*B*) *Acetophenone azine.*
(*C*) o-*Iodobenzaldehyde azine.*
(*D*) o-*Iodoacetophenone azine.*
(*E*) 3 : 8-*Dimethyl*-4 : 5-6 : 7-*dibenzo*-1 : 2-*diazocine.*
(*F*) 3 : 8-*Diethyl*-4 : 5-6 : 7-*dibenzo*-1 : 2-*diazocine.*
(*G*) 3 : 8-*Diphenyl*-4 : 5-6 : 7-*dibenzo*-1 : 2-*diazocine.*

azines.[21] *ortho*-Substituted ketazines may be expected to show a particularly strong disturbance of conjugation between the CR:N·N:CR group and attached benzene rings, since there will be difficulty in accommodating the R groups and the *ortho*-substituents in a coplanar Aryl–C=N– structure. When compared with that in benzaldehyde azine ($\lambda_{max.}$ 300 mμ), the peak in the *o*-iodo-derivative differs chiefly in being split into two subsidiary bands (Fig. 3), as has been noted in some related cases.[21a,b] On the other hand, the spectrum of acetophenone azine ($\lambda_{max.}$ 265 mμ) differs greatly from those of *o*-iodo-acetophenone azine and *o*-iodopropiophenone azine (Fig. 3), which show maxima at much shorter wavelength ($\lambda_{max.}$ 225 mμ) and resemble the spectra of the dialkyldiazocines (Fig. 2). The curve for the diphenyldiazocine resembles those of the dialkyldiazocines in the 210—230 mμ region, but it shows an extra band at 280 mμ, presumably due, as in open-chain ketazines, to conjugation in the group Ph·C:N·N:CPh.

Infrared absorption spectra [22] have been reported by Blout, Fields, and Karplus [23] for

[20] Beeby, Mann, and Turner, *J.*, 1950, 1923.
[21] (*a*) Blout and Gofstein, *J. Amer. Chem. Soc.*, 1945, **67**, 13; (*b*) Blout, Eager, and Gofstein, *ibid.*, 1946, **68**, 1983; (*c*) Ferguson and Goodwin, *ibid.*, 1949, **71**, 633; (*d*) Barany, Braude, and Pianka, *J.*, 1949, 1898; (*e*) Szmant and Planinsek, *J. Amer. Chem. Soc.*, 1950, **72**, 4981.
[22] Cf. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, p. 226.
[23] Blout, Fields, and Karplus, *J. Amer. Chem. Soc.*, 1948, **70**, 194.

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several aldazines containing the group CH:N·N:CH in conjugation with ethylenic bonds or furan rings. A sharp peak due to the C=N stretching vibration occurred in the range 1580—1670 cm.$^{-1}$ and showed a displacement towards lower frequency in proportion to the degree of conjugation in the compound; it was accompanied by neighbouring subsidiary peaks. The characteristics of our compounds are shown for this region of the spectrum in Fig. 4. The interrelations here observed are reminiscent of those discussed above for the ultraviolet region: benzaldehyde azine, acetophenone azine, and *o*-iodobenzaldehyde azine resemble one another in giving sharp peaks at 1610—1630 cm.$^{-1}$ and sharp, less intense peaks at ~1580 cm.$^{-1}$; *o*-iodoacetophenone azine and the two dialkyl-substituted diazocines are alike in exhibiting broad peaks in the 1610—1630 cm.$^{-1}$ region, with the subsidiary peak reduced to a shoulder; in the diphenyl-substituted diazocine a strong peak reappears at 1570 cm.$^{-1}$.

Experimental

o-Iodoacetophenone.—Reaction of *o*-iodobenzoyl chloride (75 g.) and diethyl ethoxymagnesiomalonate (from 0·5 g.-atom of magnesium), as described for the preparation of *o*-chloroacetophenone,[6] gave the ketone (54 g., 78%), b. p. 144°/15 mm. It was obtained in only 25% yield by reaction of *o*-iodobenzoyl chloride and ethyl sodioacetoacetate [8] and was then accompanied by much ethyl *o*-iodobenzoate. The ketone was characterised as the semicarbazone,[8] m. p. 179°, and as the *azine*, which crystallised from ethanol in colourless needles, m. p. 124° (Found: C, 39·2; H, 2·7; N, 5·4; I, 51·9. $C_{16}H_{14}N_2I_2$ requires C, 39·3; H, 2·9; N, 5·7; I, 52·0%).

2 : 2′-*Diacetyldiphenyl.*—*o*-Iodoacetophenone (49 g.) was heated under reflux in dimethylformamide (70 ml.) with copper bronze (40 g.) for 6 hr. The mixture was extracted with chloroform, and the extract distilled at 134°/0·4 mm., giving solid 2 : 2′-diacetyldiphenyl (14 g., 59%), which crystallised from hexane in needles, m. p. 92·5° (Found: C, 80·7; H, 5·5. Calc. for $C_{16}H_{14}O_2$: C, 80·7; H, 5·9%); Hall *et al.*[3] give m. p. 93—94°. In 3 hr. at 180—200°, in the absence of dimethylformamide, the diketone was obtained in 45% yield, together with acetophenone (10%).

Reaction of 2 : 2′-*Diacetyldiphenyl with Hydrazine.*—The data summarised in Table 1 (as also in Tables 2 and 3) were usually obtained with 0·5—2·0 g. of the diketone and 50—200 ml. of solvent. The following are the best conditions so far found for preparing the diazocine and 9 : 10-dimethylphenanthrene respectively.

Table 1. *Reaction of hydrazine and* 2 : 2′-*diacetyldiphenyl.*

	Temp.	Time (hr.)	Medium *	Molar ratio, N_2H_4 : diketone	Dimethylphenanthrene (yield %)	Diazocine (yield %)
(i)	−20°	96	EtOH	1·2 : 1	2	72
(ii)	0	72	EtOH	1·2 : 1	2	70
(iii)	20	24	EtOH	1·2 : 1	2	66
(iv)	78	2—6	EtOH	1·5—3 : 1	8—19	50—52
(v)	78	2	EtOH + 10N-H_2SO_4 (10 ml.)	1·1 : 1	8—12	38—42
(vi)	78	1	EtOH + KOH (0·1 g.)	3 : 1	0	0
(vii)	78	1	EtOH + NaOEt (0·2 g.)	3 : 1	0	0
(viii)	117	1	AcOH	3 : 1	21	28
(ix)	117	1	AcOH	3 : 1	21	20
(x)	136	3	Et·CO_2H	3 : 1	28	0
(xi)	180	0·5	$CH_2Cl·CO_2H$	3 : 1	21	0
(xii)	180	2	Diethylene glycol (+ anhyd. N_2H_4)	30 : 1	25	30
(xiii)	180	2	Diethylene glycol + 10N-H_2SO_4 (10 ml.)	1·1 : 1	13	35

* 60% or 100% Hydrazine hydrate was used in (i)—(iv) and (vi)—(xi), anhydrous hydrazine in (xii) only, hydrazine sulphate in (v) and (xiii). The hydrazine (in 10 ml. of solvent) was added dropwise in (ii), (iv)—(viii), and (xii).

(*a*) 2 : 2′-Diacetyldiphenyl (2·0 g., 0·0084 mole) in ethanol (200 ml.) was treated at −20° with 100% hydrazine hydrate (0·50 g., 0·010 mole) and after 1 hr. the mixture was transferred to a refrigerator and kept for 4 days at −5°. Ethanol was then evaporated under reduced

pressure at room temperature and the residue chromatographed on alumina. Elution with benzene gave a little 9 : 10-dimethylphenanthrene (0·04 g., 2%), and ether gave colourless prisms of 3 : 8-dimethyl-4 : 5-6 : 7-dibenzo-1 : 2-diazocine (1·44 g., 72%), m. p. 165°, raised to 168° by recrystallisation from hexane (Hall *et al.*[3] give m. p. 167—168°) (Found: C, 82·0; H, 6·1; N, 11·6. Calc. for $C_{16}H_{14}N_2$: C, 82·0; H, 6·0; N, 12·0%).

(*b*) 2 : 2′-Diacetyldiphenyl (0·50 g., 0·0021 mole) and 60% hydrazine hydrate (0·50 g., 0·006 mole) were heated for 2 hr. under reflux in propionic acid (30 ml.). Evaporation, followed by chromatography on alumina, yielded 9 : 10-dimethylphenanthrene (0·12 g., 27%) and yellow resin (0·30 g.) but no diazocine. The hydrocarbon had m. p. 143·5—144° after recrystallisation from methanol (Found: C, 92·9; H, 7·0. Calc. for $C_{16}H_{14}$: C, 93·2; H, 6·8%) and formed a picrate, m. p. 193—194°; Bradsher and Amore [24] give m. p. 142·5—143° and 193—194°, respectively.

Conversion of o-*Iodoacetophenone Azine into* 9 : 10-*Dimethylphenanthrene.*—2·0 g. (0·0041 mole) of the azine (see above) was heated with copper bronze (2·0 g.) at 210° for 1·5 hr. and the product extracted with ether. Chromatography of the extract (0·58 g.) on alumina gave resins and a crystalline fraction (0·07 g., 8%), which was 9 : 10-dimethylphenanthrene, m. p. and mixed m. p. 141—142°; no diazocine was detected.

Stability of 3 : 8-*Dimethyl*-4 : 5-6 : 7-*dibenzo*-1 : 2-*diazocine.*—Samples were treated under the following conditions and the products examined by chromatography.

(*a*) After 15 min. at 370—380° or for 24 hr. at 220°, unchanged diazocine (65% and 55% respectively) was recovered, but no 9 : 10-dimethylphenanthrene obtained.

(*b*) 90% of the diazocine was recovered after 36 hr. in refluxing acetic acid (0·20 g. in 20 ml.), but when the diazocine (0·20 g.) and 100% hydrazine hydrate (0·50 g., 12 mol.) were heated for 48 hr. in refluxing acetic acid (50 ml.), the unchanged diazocine (70%) was accompanied by 9 : 10-dimethylphenanthrene (23%). A similar mixture, irradiated by a 250w mercury-vapour lamp for 16 hr. at the b. p., gave 85% of unchanged diazocine and 11% of 9 : 10-dimethylphenanthrene.

(*c*) The diazocine (0·20 g.), after 24 hr. at 240° in diethylene glycol (25 ml.), was recovered (65%), together with 9 : 10-dimethylphenanthrene (6%). Under similar conditions, but with 100% hydrazine hydrate (2·5 mol.) also present, the recovery was 55% and the yield of hydrocarbon 23%.

(*d*) Heating the diazocine with hydrazine (1 mol.) in 5N-aqueous sulphuric acid gave only resins.

(*e*) Attempted hydrogenation with platinum or palladium catalyst at ordinary temperature and pressure gave unchanged diazocine as the only crystalline product. Only resins resulted from treatment with lithium aluminium hydride in ether at room temperature or with sodium amalgam and ethanol at 50°.

o-*Iodopropiophenone.*—A solution of diethyl ethoxymagnesiomethylmalonate was prepared from 0·5 g.-atom of magnesium and was treated by Bowman's procedure [6] with *o*-iodobenzoyl chloride (0·37 mole). o-*Iodopropiophenone* was obtained (72%; b. p. 96°/0·3 mm., n_D^{25} 1·5978) (Found: C, 41·6; H, 3·5. C_9H_9OI requires C, 41·5; H, 3·5%). The derived *azine* crystallised from ethanol in colourless plates, m. p. 107·5° (Found: C, 41·6; H, 3·4; N, 5·3. $C_{18}H_{18}N_2I_2$ requires C, 41·85; H, 3·5; N, 5·4%).

2 : 2′-*Dipropionyldiphenyl.*—*o*-Iodopropiophenone (65 g., 0·25 mole) and copper bronze (50 g.) were heated for 2 hr. in refluxing dimethylformamide (80 ml.), and the product taken up in chloroform. Distillation yielded 2 : 2′-*dipropionyldiphenyl* (22 g., 66%), b. p. 122—123°/0·001 mm., n_D^{25} 1·5807 (Found: C, 81·3; H, 6·5. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%).

Reaction of 2 : 2′-*Dipropionyldiphenyl with Hydrazine.*—Procedures (*a*) and (*b*) below represent the best conditions so far found (see Table 2) for preparing the diazocine and 9 : 10-diethylphenanthrene respectively. Only unchanged diketone (84%) was found when reaction was attempted with 100% hydrazine hydrate and Raney nickel W-2 in boiling ethanol, as described by Balcom and Furst [25] for the reduction of nitro-compounds.

(*a*) A solution of 2 : 2′-dipropionyldiphenyl (1·00 g., 0·0038 mole) and 100% hydrazine hydrate (0·21 g., 0·0042 mole) in ethanol (75 ml.) was left for 3 days at room temperature. Solvent was removed under reduced pressure and the residue chromatographed with benzene on alumina, yielding colourless prisms of 3 : 8-*diethyl*-4 : 5-6 : 7-*dibenzo*-1 : 2-*diazocine* (0·70 g.,

[24] Bradsher and Amore, *J. Amer. Chem. Soc.*, 1944, **66**, 1280.
[25] Balcom and Furst, *ibid.*, 1953, **75**, 4334.

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70%), m. p. 126·5°, unchanged by recrystallisation from hexane (Found: C, 82·3; H, 6·6; N, 10·8. $C_{18}H_{18}N_2$ requires C, 82·4; H, 6·9; N, 10·7%).

(*b*) Anhydrous hydrazine (2·0 g., 0·063 mole), prepared as described by Barton, Ives, and Thomas,[9] in redistilled diethylene glycol (10 ml.) was added to 2 : 2′-dipropionyldiphenyl (1·00 g.) in redistilled diethylene glycol (40 ml.), and the mixture refluxed for 2 hr. The solution

TABLE 2. *Reaction of hydrazine and* 2 : 2′*-dipropionyldiphenyl.*

	Temp.	Time (hr.)	Medium *	Molar ratio, N_2H_4 : diketone	Diethylphenanthrene (yield %)	Diazocine (yield %)
(i)	15°	72	EtOH	1·1 : 1	0	71
(ii)	78	5	EtOH	3·2 : 1	0	55
(iii)	117	3	AcOH	3·2 : 1	0	39
(iv)	136	2	Et·CO_2H	1·3 : 1	0	42
(v)	180	2	Diethylene glycol (anhyd. N_2H_4)	16 : 1	31	48
(vi)	180	2	Diethylene glycol (anhyd. N_2H_4)	16 : 1	12	51

* 100% Hydrazine hydrate was used in (i)—(iv) and was added dropwise, in 10 ml. of solvent, in (ii)—(iv); the diketone, in 10 ml. of solvent, was added dropwise to the hydrazine solution in (vi).

was poured into water, the product extracted with ether, the solvent evaporated, and the residue chromatographed on alumina. 9 : 10-Diethylphenanthrene (0·27 g., 30%) was eluted with benzene and the diazocine (0·48 g., 48%) was eluted with ether. The 9 : 10-diethylphenanthrene had m. p. 103° when recrystallised from methanol; Zincke and Tropp [2] give m. p. 105—106° (Found: C, 92·3; H, 7·9. Calc. for $C_{18}H_{18}$: C, 92·3; H, 7·7%). Difficulty was experienced in preparing a picrate but the *styphnate* was obtained in orange needles, m. p. 155·5° from benzene–hexane (Found: C, 60·0; H, 4·3; N, 9·0. $C_{24}H_{21}O_8N_3$ requires C, 60·1; H, 4·4; N, 8·8%).

Stability of 3 : 8-*Diethyl*-4 : 5-6 : 7-*dibenzo*-1 : 2-*diazocine.*—A solution of the diazocine (200 mg., 0·76 mmole) and excess of 100% hydrazine hydrate (500 mg., 0·01 mole) in diethylene glycol (25 ml.) was kept for 24 hr. at 210°. Dilution with water, extraction with ether, and chromatography yielded unchanged diazocine (150 mg.) and 9 : 10-diethylphenanthrene (20 mg., 11%). In the same solvent, in 24 hr. at 240°, but without hydrazine, no hydrocarbon was obtained and 160 mg. of diazocine were recovered.

o-*Iodobenzophenone.*—*o*-Iodobenzoyl chloride (50 g.) in dry benzene (200 ml.) was gradually treated with powdered anhydrous aluminium chloride (28 g.), and the mixture refluxed for 2 hr. After hydrolysis of the complex, *o*-iodobenzophenone was obtained as a nearly colourless liquid (34 g., 59%), b. p. 143°/0·3 mm., which solidified and gave needles, m. p. 32·5°, from hexane (Found: C, 51·0; H, 3·0. Calc. for $C_{13}H_9OI$: C, 50·6; H, 2·9%); Montagne [26] gives b. p. 210—211°/13 mm., m. p. 32°.

2 : 2′-*Dibenzoyldiphenyl.*—*o*-Iodobenzophenone (20 g., 0·065 mole), copper bronze (18 g.), and dimethylformamide (40 ml.) were heated under reflux for 2 hr., the product was taken up in chloroform, the solvents were removed, and the solid residue was recrystallised from light petroleum (b. p. 100—120°), yielding 9·0 g. (76%) of 2 : 2′-dibenzoyldiphenyl in needles, m. p. 167°, raised to 171° by further recrystallisation from *cyclo*hexane (Found: C, 86·1; H, 4·9. Calc. for $C_{26}H_{18}O_2$: C, 86·2; H, 5·0%); De Tar and Sagmanli [27] give m. p. 166·5—168°.

Reaction of 2 : 2′*-Dibenzoyldiphenyl with Hydrazine.*—Procedures (*a*) and (*b*) below represent the best conditions so far found (see Table 3) for converting the diketone into the diazocine and 9 : 10-diphenylphenanthrene respectively.

(*a*) 2 : 2′-Dibenzoyldiphenyl (0·50 g., 0·00138 mole) and 100% hydrazine hydrate (2·0 g., 0·04 mole) were heated in diethylene glycol (40 ml.) at 180° for 72 hr. The cooled solution was diluted with water and extracted with ether and the extract was chromatographed with benzene on alumina. 9 : 10-Diphenylphenanthrene (0·12 g., 26%) was obtained, followed by 3 : 8-*diphenyl*-4 : 5-6 : 7-*dibenzo*-1 : 2-*diazocine* (0·30 g., 60%), in colourless prisms, m. p. 228—229°, raised to 232° by recrystallisation from hexane (Found: C, 87·3; H, 5·0; N, 7·9. $C_{26}H_{18}N_2$ requires C, 87·2; H, 5·0; N, 7·8%).

(*b*) 2 : 2′-Dibenzoyldiphenyl (0·50 g.) and anhydrous hydrazine [9] (2·0 g., 0·063 mole) in redistilled diethylene glycol (40 ml.) were kept at 180° for 48 hr. and the product was treated as in (*a*). 9 : 10-Diphenylphenanthrene was obtained as needles (0·39 g., 86%); m. p. 238°,

[26] Montagne, *Rec. Trav. chim.*, 1915, **34**, 156.
[27] DeTar and Sagmanli, *J. Amer. Chem. Soc.*, 1950, **72**, 965.

unchanged by recrystallisation from hexane (Found: C, 94·7; H, 5·2. Calc. for $C_{26}H_{18}$: C, 94·6; H, 5·4%); Schoepfle and Ryan [28] give m. p. 235°.

TABLE 3. *Reaction of hydrazine and 2 : 2′-dibenzoyldiphenyl.*

	Temp.	Time (hr.)	Conditions *	Mol. ratio, N_2H_4 : diketone	Diketone recovered (%)	Diphenylphenanthrene (yield %)	Diazocine (yield %)
(i)	78°	5	Boiling EtOH	1·3 : 1	97	0	0
(ii)	117	20	Boiling AcOH	1·5 : 1	98	0	0
(iii)	180	72	Diethylene glycol	30 : 1	0	26	60
(iv)	180	48	Diethylene glycol; anhyd. N_2H_4	45 : 1	0	86	0
(v)	200	24	EtOH; 100 ml. stainless-steel autoclave	2·6 : 1	58	9	0
(vi)	270—290	24	,, ,,	2·2 : 1	0	18	0
(vii)	200	6	AcOH; 100 ml. stainless-steel autoclave	7·2 : 1	0	22	0
(viii)	200	12	,, ,,	3·6 : 1	0	35	0
(ix)	280—290	5	,, ,,	3·6 : 1	0	29	0
(x)	200—230	6	AcOH; sealed Pyrex tube	7·2 : 1	44	20	0

* 100% Hydrazine hydrate was used except in (iv).

Spectra.—Ultraviolet absorption spectra (Fig. 1 and 2) were examined in a Unicam S.P. 500 quartz spectrometer, for solutions in *n*-hexane or *cyclo*hexane. Infrared absorption spectra were examined in a Perkin-Elmer double-beam spectrometer, for 5% solutions in carbon disulphide and in carbon tetrachloride, and also for pressed potassium bromide discs. Strong peaks were recorded as follows: benzaldehyde azine, at 1630, 1580, 1496, 1451, 747, and 685 cm.$^{-1}$; acetophenone azine, at 1609, 1579, 1500, 1450, 1361, 754, and 686 cm.$^{-1}$; *o*-iodobenzaldehyde azine, at 1616, 1585, 1560, 1460, 1436, and 744 cm.$^{-1}$; *o*-iodoacetophenone azine, at 1626, 1434, 1363, and 753 cm.$^{-1}$; 3 : 8-dimethyl-4 : 5-6 : 7-dibenzo-1 : 2-diazocine, at 1628, 1435, 1371, and 746 cm.$^{-1}$ (weaker bands at 767, 760, 753, and 735 cm.$^{-1}$); 3 : 8-diethyl-4 : 5-6 : 7-dibenzo-1 : 2-diazocine, at 1611, 1477, 1461, 1440, 1375, and 738 cm.$^{-1}$ (weaker bands at 767, 762, 753, and 744 cm.$^{-1}$); 3 : 8-diphenyl-4 : 5-6 : 7-dibenzo-1 : 2-diazocine, at 1602, 1570, 1558, 1445, 743, and 683 cm.$^{-1}$ (weaker bands at 771, 762, 753, and 738 cm.$^{-1}$).

We thank the Chemical Society for a grant from the Research Fund.

THE QUEEN'S UNIVERSITY, BELFAST. [*Received, November 14th*, 1957.]

[28] Schoepfle and Ryan, *J. Amer. Chem. Soc.*, 1932, **54**, 3687.

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278. *Nucleotides. Part XLIV.* Thymidine-5′ Pyrophosphate and Triphosphate.*

By MRS. B. E. GRIFFIN and SIR ALEXANDER TODD.

Thymidine-5′ pyrophosphate has been obtained in 70% yield starting from 3′-*O*-benzylthymidine by converting it into 3′-*O*-benzylthymidine-5′ benzyl phosphorochloridate, condensing this with a salt of benzyl dihydrogen phosphate, and subsequently removing protecting groups. Thymidine-5′ triphosphate was similarly prepared in over 40% yield from the same phosphorochloridate by reaction with a salt of P^1P^2-dibenzyl pyrophosphate, followed by debenzylation.

THE importance of deoxyribonucleoside polyphosphates in certain biological systems [1] makes their preparation by chemical methods desirable, partly to aid in the characterisation of the naturally occurring materials and more particularly to render them more available

* Part XLIII, *J.*, 1958, 546.

[1] Potter and Schlesinger, *J. Amer. Chem. Soc.*, 1955, **77**, 6714; Klenow and Lichtler, *Biochim. Biophys. Acta*, 1957, **23**, 6.

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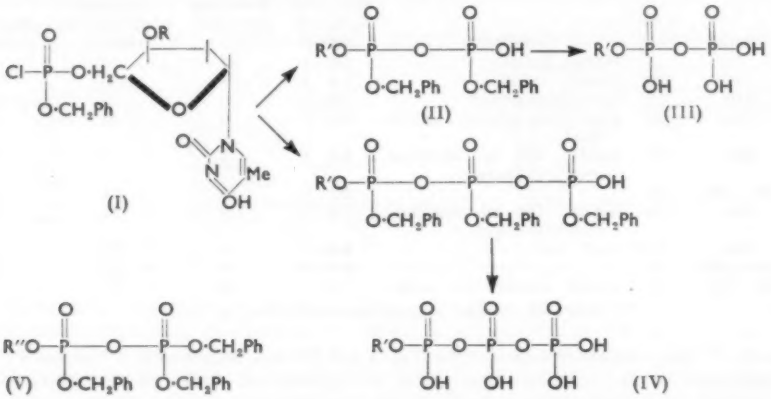
for use in the study of enzyme systems. We now report one stage of our investigations in this field, namely, convenient preparations of thymidine-5′ pyrophosphate (III; R′ = thymidine-5′) and triphosphate (IV; R′ = thymidine-5′); we believe them to represent an improvement on those employing carbodi-imides.[2]



In endeavouring to prepare thymidine-5′ pyrophosphate we first applied the method used by Kenner, Todd, and Weymouth[3] in their synthesis of uridine-5′ pyrophosphate (UDP). 3′-*O*-Acetylthymidine-5′ benzyl phosphorochloridate (I; R = Ac), prepared from the known 3′-acetylthymidine,[4] was condensed with a salt of dibenzyl hydrogen phosphate and the product was debenzylated by short treatment with *m*-cresol,[5] followed by hydrogenolysis. Unfortunately, removal of the residual acetyl group under alkaline conditions was accompanied by considerable breakdown of the pyrophosphate linkage and the yield of thymidine-5′ pyrophosphate (III; R′ = thymidine-5′) was low. Since benzyl ethers of nucleosides can be cleaved by hydrogenation,[6] we sought to improve the preparation by using 3′-*O*-benzylthymidine (prepared from 5′-*O*-tritylthymidine by benzylation and removal of the trityl residue) in place of 3′-*O*-acetylthymidine in the above preparation. Debenzylation was effected as before by treatment with *m*-cresol followed by hydrogenation; a somewhat higher yield (*ca.* 25%) of thymidine-5′ pyrophosphate was obtained, but the crude product contained in addition large quantities of thymidine-5′ phosphate and inorganic pyrophosphate which made purification by ion-exchange chromatography very difficult. These by-products undoubtedly arise from reaction of the fully esterified initial product (V; R″ = 3′-*O*-benzylthymidine-5′) with dibenzyl phosphate anion, leading to the formation of 3′-*O*-benzylthymidine-5′ benzyl phosphate and tetrabenzyl pyrophosphate. Such exchange reactions of fully esterified pyrophosphates are well known and an example of a similar type has recently been discussed by Kenner, Reese, and Todd[7] in connection with the synthesis of P^1-adenosine-5′ P^2-uridine-5′ pyrophosphate.

These findings suggested that better results in syntheses of this nature might be achieved by using salts of monobenzyl phosphate rather than of dibenzyl phosphate in the initial reaction since the product would be only a triply esterified pyrophosphate of type (II), and, as such, less likely to undergo an exchange reaction leading to ultimate production of inorganic pyrophosphate. This proved to be so, and condensation of 3′-*O*-benzylthymidine-5′ benzyl phosphorochloridate (I; R = CH_2Ph) with benzyl triethylammonium

[2] Potter, Schlesinger, Buettner-Janusch, and Thompson, *J. Biol. Chem.*, 1957, **226**, 381.
[3] Kenner, Todd, and Weymouth, *J.*, 1952, 3675.
[4] Michelson and Todd, *J.*, 1953, 951.
[5] Kenner, Todd, Webb, and Weymouth, *J.*, 1954, 2288.
[6] Michelson and Todd, *J.*, 1956, 3459.
[7] Kenner, Reese, and Todd, *J.*, 1958, 546.

hydrogen phosphate, followed by debenzylation, gave thymidine-5′ pyrophosphate in 70% yield, uncontaminated by inorganic pyrophosphate and containing only traces of orthophosphate. Ion-exchange chromatography was unnecessary, the product being precipitated directly in a pure state as its calcium salt. It may be noted that Michelson and Todd [6] mention a preparation of uridine-5′ pyrophosphate (UDP) by the same type of reaction although as the experiment was carried out only to verify the nature of the phosphorochloridate used, no details of yield were given.

We then applied an analogous procedure to the preparation of thymidine-5′ triphosphate (IV; R = thymidine-5′). 3′-*O*-Benzylthymidine-5′ benzyl phosphorochloridate (I; R = CH_2Ph) was condensed with a salt of P^1P^2-dibenzyl pyrophosphate, and the product was debenzylated as before. The crude product, which contained some thymidine-5′ phosphate, thymidine-5′ pyrophosphate, and inorganic pyrophosphate, as well as the desired triphosphate, was purified by ion-exchange chromatography and isolated as barium thymidine-5′ triphosphate; the yield was 43%, based on 3′-*O*-benzylthymidine.

Experimental

Thymidine-5′ Pyrophosphate from 3′-O-Acetylthymidine.—A solution of 3′-*O*-acetylthymidine [4] (1 mol.) was treated with *O*-benzylphosphorous *OO*-diphenylphosphoric anhydride (2 mols.) as described by Kenner, Todd, and Weymouth,[3] and the crude phosphite purified by precipitation from chloroform solution; it was obtained as a yellow gum which on paper chromatography (Whatman No. 1 paper; saturated butan-1-ol–water; ascending chromatogram) showed a single ultraviolet-absorbing spot of R_P 0·70.

A mixture of this phosphite (0·67 g., 1 mol.) and *N*-chlorosuccinimide (0·21 g., 1 mol.) in benzene (15 c.c.) and methyl cyanide (1·5 c.c.) was set aside for 2 hr. at room temperature. Dibenzyl hydrogen phosphate (0·42 g., 1 mol.) and triethylamine (0·15 g., 1 mol.) were added; precipitation of triethylamine hydrochloride set in at once. The mixture was stirred for 3 hr., then washed successively with water, aqueous potassium hydrogen carbonate, N/50-hydrochloric acid, and again water, dried (Na_2SO_4), and evaporated to a straw-coloured oil. The oil was heated at 70° for 15 min. with *m*-cresol (3 c.c.), then cooled, water (20 c.c.) was added and *m*-cresol removed by ether-extraction. The aqueous solution was adjusted to pH 6—7 with 0·1N-barium hydroxide and hydrogenated (6 hr.) at room temperature and atmospheric pressure in presence of palladous oxide–palladised charcoal. Electrophoretic examination of the filtered solution in sodium acetate buffer (pH 4·8) indicated two main components, apparently the 5′-phosphate and rather more of the 5′-pyrophosphate of 3′-acetylthymidine.

Deacetylation was effected by adjusting the solution to pH 10 with barium hydroxide and maintaining it at this pH for 2—3 days. Paper chromatography (see below) showed two main ultraviolet-absorbing constituents corresponding to thymidine-5′ phosphate and pyrophosphate. By means of anion-exchange chromatography (as described below) thymidine-5′ pyrophosphate was obtained as a lithium salt (100 mg., 16%) which was free from other nucleotides but contained inorganic phosphate.

3′-O-*Benzylthymidine.*—Benzyl chloride (4·5 c.c.) and powdered potassium hydroxide (9 g.) were added to a solution of 5′-tritylthymidine [4] (3 g.) in benzene (30 c.c.) and dioxan (10 c.c.) and the mixture was refluxed for 4 hr. with vigorous stirring. Water (30 c.c.) was added to the cooled mixture, which was then neutralised with acetic acid. The benzene layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The crude oily product was twice redissolved in benzene and precipitated with light petroleum (b. p. 60—80°) before being refluxed for 10 min. with aqueous 80% acetic acid (15 c.c.) to remove the 5′-trityl group. The acetic acid solution was then set aside at room temperature for several hours. Precipitated triphenylmethanol was removed and washed with cold aqueous 80% acetic acid (5 c.c.), and the combined filtrate and washings were poured into ice-water (300 c.c.). The milky solution was concentrated *in vacuo* below 30°; colourless needles began to be formed when about half of the liquid had been removed. Evaporation was continued until the bulk of solution was reduced to 15 c.c., then the crystalline product was collected, washed with cold water, and dried. Recrystallised from acetone–*n*-heptane, 3-O-*benzylthymidine* formed colourless needles (1·3 g., 64%),

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m. p. 148—150° (Found: C, 61·6; H, 6·0; N, 8·4. $C_{17}H_{20}O_5N_2$ requires C, 61·4; H, 6·1; N, 8·4%).

Thymidine-5′ Pyrophosphate from 3′-O-Benzylthymidine.—(a) *Use of dibenzyl hydrogen phosphate.* 3′-*O*-Benzylthymidine (1 g.) was converted into its 3′-*O*-benzylthymidine-5′ benzyl phosphite as described above for the 3′-*O*-acetyl derivative, and the product was dissolved in benzene (20 c.c.) and methyl cyanide (2 c.c.). *N*-Chlorosuccinimide (0·37 g.) was added and the mixture set aside for 2 hr., moisture being excluded. A solution of dibenzyl hydrogen phosphate (0·78 g.) and triethylamine (0·4 c.c.) in benzene (10 c.c.) was added dropwise with stirring, and stirring was continued for a further 2 hr. The mixture was washed successively with water, potassium hydrogen carbonate solution, N/50-hydrochloric acid, and water, dried (Na_2SO_4), and evaporated to a thick oil. The oil was partially debenzylated with *m*-cresol as described above and debenzylation was completed by hydrogenation at room temperature and atmospheric pressure in aqueous solution at pH 3·5—4 (palladium black). The resulting solution (50 c.c.) was adsorbed on a column of anion-exchange resin (Dowex-2, chloride form; 10 × 1·5 cm.). Thymidine-5′ phosphate was eluted with 0·01N-hydrochloric acid, and 0·01N-hydrochloric acid containing lithium chloride (0·1M) eluted thymidine-5′ pyrophosphate free from other nucleotidic material (paper chromatography). The eluted thymidine-5′ pyrophosphate was isolated as lithium salt (315 mg., 25%) but paper chromatography showed that it contained a considerable amount of inorganic pyrophosphate (molybdate spray).[8] To remove inorganic pyrophosphate the crude lithium salt (80 mg.) was converted into the barium salt, then precipitated under controlled pH conditions as described for the analogous uridine-5′ pyrophosphate.[9] Barium pyrophosphate was precipitated below pH 4, and after adjustment to pH 6 *barium thymidine-5′ pyrophosphate* was precipitated as a white powder by addition of ethanol (5 vol.). Several such precipitations were necessary to obtain the barium salt (40 mg.) free from inorganic material (Found in material dried at room temperature/1 mm. over P_2O_5: C, 18·2; H, 3·4; N, 4·3; total P, 9·5, 9·7; acid-labile P, 4·8. $C_{10}H_{13}O_{11}N_2P_2Ba_{1\cdot5},3H_2O$ requires C, 18·2; H, 2·9; N, 4·3; total P, 9·4; acid-labile P, 4·7%).

(b) *Use of benzyl dihydrogen phosphate.* To a solution of 3′-*O*-benzylthymidine-5′ benzyl phosphorochloridate (prepared as described above from 0·16 g. of 3′-*O*-benzylthymidine) in benzene (10 c.c.) and methyl cyanide (1 c.c.), benzyl dihydrogen phosphate [10] (87 mg.) and triethylamine (0·13 c.c.) were added. The mixture was stirred for 2 hr., filtered from triethylamine hydrochloride, and evaporated. The thick oil obtained was examined by paper chromatography in solvent system A (see below) and showed a single ultraviolet-absorbing spot (R_F 0·89). A solution of the oil in water (20 c.c.) was brought to pH 3·4 with acetic acid and hydrogenated (16 hr.) at room temperature and atmospheric pressure (palladium black). Catalyst was filtered off and the filtrate (which appeared to contain thymidine-5′ pyrophosphate as the sole ultraviolet-absorbing constituent) was brought to pH 6 with aqueous lithium hydroxide; the lithium salt of thymidine-5′ pyrophosphate (100 mg.) was precipitated as a white powder by addition of acetone (100 c.c.). Evaporation, to small bulk, of the mother-liquor left after removal of this salt and addition of acetone yielded a further quantity (35 mg.) of product of similar purity. The yield of the lithium salt at this stage was *ca.* 70% based on 3′-*O*-benzylthymidine and paper chromatography showed that although it contained a small amount of orthophosphate it was free from inorganic pyrophosphate.

For analysis *calcium thymidine-5′ pyrophosphate* was prepared from the lithium salt by dissolution in water (5 c.c.) and addition of hydrochloric acid (to pH 2) and then calcium chloride (60 mg.); a small amount of orthophosphate was removed by adding calcium hydroxide (to pH 6) and filtering, and the calcium salt was then precipitated from the filtrate by adding 3 : 1 acetone–ethanol (50 c.c.). The salt was washed first with acetone–ethanol, then ether, and dried at room temperature (Found, in air-dried material: C, 20·3; H, 3·8; N, 4·7; P, 10·4, 10·7. $C_{10}H_{13}O_{11}N_2P_2Ca_{1\cdot5},7H_2O$ requires C, 20·5; H, 4·6; N, 4·8; P, 10·6%).

Thymidine-5′ Triphosphate.—Diammonium P^1P^2-dibenzyl pyrophosphate [11] was converted into the di(phenyltrimethylammonium) salt by passing an aqueous solution (30 c.c.) through a column of Dowex-50 ion-exchange resin (5 × 1·5 cm.) in the phenyltrimethylammonium form. Evaporation of the solution gave a thick oil which was dried by azeotropic distillation with

[8] Hanes and Isherwood, *Nature*, 1949, **164**, 1107.
[9] Anand, Clark, Hall, and Todd, *J.*, 1952, 3665.
[10] Chase, Kenner, Todd, and Webb, *J.*, 1956, 1371.
[11] Clark, Kirby, and Todd, *J.*, 1957, 1497.

benzene, then dissolved in methyl cyanide and filtered from a small amount of insoluble material. The salt, which was obtained as exceedingly hygroscopic needles by evaporating the methyl cyanide solution, was not analysed but used directly in the following experiment.

A solution of 3′-*O*-benzylthymidine-5′ benzyl phosphorochloridate [prepared from 3′-*O*-benzylthymidine (332 mg., 1 mol.) as described above] in benzene (10 c.c.) and methyl cyanide (1 c.c.) was added to solution of di(phenyltrimethylammonium) P^1P^2-dibenzyl pyrophosphate (940 mg., 1·5 mol.) in methyl cyanide (4 c.c.). The mixture was stirred at room temperature for 2 hr., then filtered, the residue was washed with 3 : 1 benzene–methyl cyanide (5 c.c.), and the combined filtrate and washings were evaporated *in vacuo* to a thick oil. Water (20 c.c.) was added, and the resulting solution brought to pH 3·5 with acetic acid and then hydrogenated (24 hr.) in the usual way with palladium black. Paper chromatography of the filtered hydrogenation solution showed that it contained as major solute a material with the properties expected of thymidine-5′ triphosphate together with some thymidine-5′ phosphate, inorganic pyrophosphate, and a trace of thymidine-5′ pyrophosphate. The solution (50 c.c.) was adjusted to pH 6 with ammonia and put on a column of Dowex-2 resin (chloride form; 8 × 2·5 cm.). Elution with 0·01N-hydrochloric acid containing lithium chloride (0·1M) removed most of the impurities, and the triphosphate was then eluted with 0·01N-hydrochloric acid containing a larger amount (0·2M) of lithium chloride. Elution was followed by examination of ultraviolet absorption, and appropriate fractions were combined, brought to pH 6 with lithium hydroxide, and concentrated to *ca.* 30 c.c. *in vacuo* below 30°. A concentrated aqueous solution of barium acetate (300 mg.) was then added, followed by ethanol (150 c.c.), and the mixture was set aside at 0° overnight. The separated barium salt was centrifuged off, washed with water (2 × 5 c.c.), to remove barium acetate, then with 1 : 1 aqueous ethanol (10 c.c.), finally with ethanol and ether, and dried. The white powder so obtained (363 mg., 43% based on 3′-*O*-benzylthymidine) ran as a single ultraviolet-absorbing spot on paper chromatography and contained only traces of inorganic pyrophosphate (molybdate spray) as impurity.

To obtain a sample for analysis, the above salt was dissolved in cold N-hydrochloric acid, and the solution brought to pH 3·5 with barium hydroxide. The precipitate contained all the inorganic impurity as well as a substantial amount of the triphosphate. It was filtered off and the filtrate brought to pH 6 with barium hydroxide and diluted with alcohol (3 vol.). The white precipitate of hydrated *barium thymidine-5′ triphosphate* was collected, washed with ethanol, then ether, and dried (Found, in air-dried material: C, 14·2; H, 2·7; N, 3·2; total P, 11·2; acid-labile P, 7·3. $C_{10}H_{13}O_{14}N_2P_3Ba_2,5H_2O$ requires C, 14·2; H, 2·8; N, 3·3; total P, 11·0; acid-labile P, 7·4%).

Paper-chromatographic and Electrophoretic Data.—Ascending chromatograms on Whatman No. 1 paper were used with solvent systems A, butan-1-ol–acetic acid–water (5 : 2 : 3), and B, *iso*butyric acid–N-ammonia–0·1M-ethylenediaminetetra-acetic acid (100 : 60 : 1·6). The results of electrophoresis in 0·1M-potassium dihydrogen phosphate on Whatman No. 4 paper at 300 v during 8 hr. are tabulated:

	R_P in system		Distance travelled (cm.) on electrophoresis
	A	B	
Thymidine-5′ phosphate	0·30	0·42	5·0
Thymidine-5′ pyrophosphate	0·20	0·28	8·4
Thymidine-5′ triphosphate	0·10	0·22	10·0

We gratefully acknowledge the award of a Marshall Scholarship which enabled one of us (B. E. G.) to take part in this work.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 26th*, 1957.]

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279. *Magnetic Studies with Copper(II) Salts. Part III.*[1] *The Constitution of Copper(II) n-Alkanoates in Solution.*

By R. L. Martin and Alice Whitley.

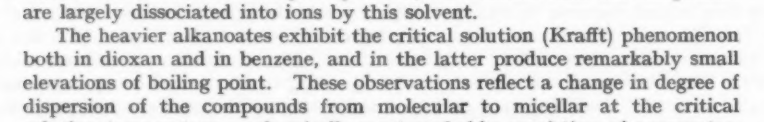
The anomalously low room-temperature magnetic moments observed for powdered copper(II) salts of straight-chain alkanoic acids [1] are shown to persist in dioxan and in benzene solutions. The solutions are non-conductors of electricity, and cryoscopic measurements indicate that the salts, when soluble, are dimeric in dioxan. Spectrophotometric studies in the visible and the near ultraviolet region reveal that, in addition to the familiar "copper band" occurring at *ca.* 7000 Å, the solutions are characterised by a well-defined absorption band at 3750 Å. These observations leave little doubt that the compounds retain their binuclear configuration in the above solvents, and unambiguously establish that exchange demagnetisation in copper *n*-alkanoates is intramolecular rather than intermolecular.

In contrast, magnetic, electrical conductivity, cryoscopic, and spectrophotometric measurements in aqueous solutions demonstrate that the binuclear structure is destroyed by water, and confirm that the compounds are largely dissociated into ions by this solvent.

The heavier alkanoates exhibit the critical solution (Krafft) phenomenon both in dioxan and in benzene, and in the latter produce remarkably small elevations of boiling point. These observations reflect a change in degree of dispersion of the compounds from molecular to micellar at the critical solution temperature, each micelle most probably consisting of aggregates, $[Cu_2(R{\cdot}CO_2)_4]_n$, of binuclear molecules, bound together by weak polar forces in conjunction with residual attractive forces between peripheral hydrocarbon chains.

Copper formate has been obtained in the binuclear configuration for the first time, in the form of a dioxan complex which has a particularly low magnetic moment, $\mu \sim 1$ B.M.

Previously [1,2] it was shown that a number of copper(II) salts of *n*-alkanoic acids exhibit a temperature variation of their magnetic susceptibility which is anomalous in the sense that antiferromagnetic rather than Curie-law behaviour is observed. The shapes of all the susceptibility–temperature curves were so closely similar that it was suggested that, in the solid state, copper *n*-alkanoates adopt the acetate-type binuclear configuration (I) rather than the uninuclear structure (II). If this postulate is correct, the anomalous magnetic behaviour is readily understood in terms of intramolecular exchange interaction between contiguous copper atoms within each binuclear molecule.



However, an alternative suggestion, favouring structure (II), was made by Gilmour and Pink,[3] to account for the anomalous magnetic behaviour of copper laurate, namely, that supposedly planar laurate molecules stack crystallographically to form layers of copper atoms separated by fatty acid groups extending in both directions. They further suggested

[1] Part II, Martin and Waterman, *J.*, 1957, 2545.
[2] Figgis and Martin, *J.*, 1956, 3837.
[3] Gilmour and Pink, *J.*, 1953, 2198.

that the resulting intermolecular exchange interaction would be antiferromagnetic and thus account for both the diminished susceptibility and its anomalous temperature dependence. Although they too now [4] favour structure (I) for copper laurate, it remains important to examine their earlier postulate in more detail. Furthermore, it is of interest to elucidate the constitution of these compounds both in non-ionising and in aqueous solvents.

A crucial test for the binuclear structure lies in ascertaining whether the magnetic moment will remain quenched when the possibility of intermolecular exchange is removed by dissolving the compounds in solvents such as dioxan or benzene. If the binuclear structure (I) is present in solution, intramolecular exchange will persist and the magnetic moment will remain diminished. If, on the other hand, the uninuclear structure (II) is favoured, all copper–copper interactions will be eliminated and the moment will rise to the value usually observed for magnetically dilute copper(II) compounds.

An additional stringent test is obviously provided by molecular-weight determinations in the above solvents. Another criterion has been recently provided by Tsuchida and Yamada [5,6] who suggest that the presence of an absorption band at 3750 Å in chloroform or alcohol solutions of these compounds is diagnostic for the binuclear structure.

With these objects in mind, magnetic, cryoscopic, and spectrophotometric measurements have been made of solutions in dioxan, benzene, and water. In addition, the electrical conductivity of the aqueous solutions has been determined to verify ionic dissociation in this solvent. The compounds selected were the copper(II) salts of formic, acetic, propionic, butyric, valeric, lauric, stearic, and behenic acids, *i.e.*, $H{\cdot}[CH_2]_n{\cdot}CO_2H$, where $n = 0$, 1, 2, 3, 4, 11, 17, and 21, these being salts of acids available very pure and providing a range adequate to interpolate properties of intermediate members.

Experimental

Materials.—The preparation of copper(II) salts of acetic, propionic, butyric, lauric, stearic, and behenic acids has been described.[1,2] Copper formate tetrahydrate was prepared by treating Merck's " purissimus " grade copper carbonate with an excess of the diluted acid and allowing the solution to crystallise (Found: C, 10·7; H, 4·50; Cu, 28·1; H_2O, 32·0. Calc. for $CuC_2H_2O_4,4H_2O$: C, 10·6; H, 4·47; Cu, 28·2; H_2O, 31·9%). The anhydrous salt was prepared by dehydration at 100° over phosphoric oxide in a vacuum pistol (Found: C, 15·6; H, 1·25; Cu, 41·3. Calc. for $CuC_2H_2O_4$: C, 15·6; H, 1·31; Cu, 41·4%).

Copper valerate was prepared by metathesis of aqueous copper acetate with an alcoholic solution of valeric acid. Blue-green needle-shaped crystals of the anhydrous valerate were slowly deposited (Found: C, 44·9; H, 6·6; Cu, 24·1. Calc. for $CuC_{10}H_{18}O_4$: C, 45·2; H, 6·8; Cu, 23·9%).

The degree of hydration, colour, and solubility of copper alkanoates is relevant. The pale blue formate with a magnetic moment, $\mu \sim 1{\cdot}6$ B.M., considerably higher than those of its blue-green homologues, $\mu \sim 1{\cdot}38$ B.M., crystallises as a tetrahydrate, in marked contrast to the acetate, propionate, butyrate, and valerate,[6] which all crystallise as monohydrates. It was found that copper butyrate can also crystallise as a dihydrate if the mother-liquor is dilute with respect to butyric acid. However, the dihydrate readily loses one water molecule under mild dehydrating conditions (*e.g.*, standing over $CaCl_2$), whereas vacuum drying (over P_2O_5) at 100° is required for complete dehydration of the monohydrate. Hence, it is concluded that the dihydrate should be formulated as the hydrated aquo-complex, $[Cu_2(C_3H_7{\cdot}CO_2)_4(H_2O)_2],2H_2O$. The laurate, stearate, and behenate are anhydrous.

The formate, acetate, propionate, and butyrate are soluble in water giving blue solutions which are much more intensely coloured than solutions containing hexaquocupric ions, *e.g.*, $Cu(ClO_4)_2$. The valerate is barely soluble (*ca.* 0·0005M), and the laurate, stearate, and behenate quite insoluble.

[4] Herron and Pink, *J.*, 1956, 3948.
[5] Tsuchida and Yamada, *Nature*, 1955, **176**, 1171.
[6] Tsuchida, Yamada, and Nakamura, *Nature*, 1956, **178**, 1192.

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The solubility behaviour of these salts in benzene is remarkable. At room temperature, only the butyrate and valerate are slightly soluble. However, the butyrate and higher homologues readily dissolve in warm benzene to give blue-green solutions. The solutions of the butyrate and valerate are stable for some hours when cooled to room temperature, whereas the laurate, stearate, and behenate are immediately reprecipitated from solution in a very finely divided form. Although quantitative determinations of solubility were not made, it was apparent that the heavier alkanoates are practically insoluble below a critical solution temperature (C.S.T.), but when this temperature is reached their solubilities increase tremendously. Similar behaviour has previously been observed with toluene solutions of copper laurate [7] and copper stearate.[8]

Since the insolubility of copper alkanoates in benzene severely restricted our proposed magnetic and cryoscopic studies, a more effective solvent was sought. Dioxan was particularly suitable, for, in addition to having convenient cryoscopic properties, it dissolves the formate, acetate, propionate, butyrate, and valerate at room temperature, forming blue-green solutions; the laurate, stearate, and behenate, however, exhibit the critical solution phenomenon in this solvent. In boiling dioxan the alkanoates undergo some decomposition, the colour of the solutions changing to green, and in several cases (*e.g.*, copper butyrate) colloidal particles are formed. The C.S.T.'s were roughly determined by gradually warming copper alkanoate–solvent mixtures and estimating visually the onset of solubility; the data are contained in Table 1.

TABLE 1. *Critical solution temperatures for copper*(II) n-*alkanoates dissolved in benzene and in dioxan.*

Compound		$Cu(C_{11}H_{23}\cdot CO_2)_2$	$Cu(C_{17}H_{35}\cdot CO_2)_2$	$Cu(C_{21}H_{43}\cdot CO_2)_2$
C.S.T. in	dioxan	37°	43°	60°
	benzene	62°	64°	72°

Magnetic Measurements.—The magnetic properties of copper alkanoates in solution were examined by the Gouy method, three solvents, water, benzene, and dioxan, being used. Water, doubly distilled in an all-silica still, and " AnalaR " benzene, which was repeatedly recrystallised and carefully fractionated, were used as calibrating liquids. Their specific gram-susceptibilities were taken as $\chi_g(H_2O) = -0{\cdot}720 \times 10^{-6}$ (20°) and $\chi_g(C_6H_6) = -0{\cdot}702 \times 10^{-6}$ (20°). The 1 : 4-dioxan (B.D.H. " Specially Pure " quality) was dried (Na) and used without further purification. Samples taken from different bottles consistently gave susceptibilities in the range $\chi_g(C_4H_8O_2) = -0{\cdot}587$ to $-0{\cdot}590 \times 10^{-6}$ (20°).

The specific gram-susceptibility of each solution was calculated from an expression used by French and Trew,[9] *viz.*,

$$\chi_{solution} = \left\{\chi_{solvent} - \frac{k_{air}}{d_{solvent}}\right\}\left\{\frac{d_{solvent} \times F_{solution}}{d_{solution} \times F_{solvent}}\right\} + \frac{k_{air}}{d_{solution}}$$

where χ is specific gram-susceptibility, k_{air} the volume susceptibility of air ($0{\cdot}0294 \times 10^{-6}$), and d the density measured in a bicapillary dilatometer at the temperature of the magnetic measurements. The resultant thrust, F(mg.), was produced by a magnetic field of *ca.* 5000 gauss acting on an 11 cm. column of liquid contained in a stoppered Pyrex tube. The gram-susceptibility of the dissolved copper salt χ_g(salt) was then obtained by application of Weidemann's mixture equation:

$$\chi_g(\text{salt}) = \{\chi_{solution} - (1 - \theta)\chi_{solvent}\}/\theta$$

where θ represents the weight-fraction of copper salt in solution. The resulting magnetic data (corrected both for the underlying diamagnetism of all atoms, Δ, and for the temperature-independent paramagnetism of copper as previously described [1, 2]) are in Table 2.

Molecular-weight Determinations.—The determination of molecular weights for copper alkanoates dissolved in water, benzene, and dioxan, by conventional ebullioscopic and cryoscopic methods, was beset with a number of experimental difficulties. Of these, partial

[7] Nelson and Pink, *J.*, 1952, 1744.
[8] E. P. Martin and Pink, *J.*, 1948, 1750.
[9] French and Trew, *Trans. Faraday Soc.*, 1945, **41**, 439.

decomposition in boiling dioxan, critical solution behaviour in both benzene and dioxan, and the great affinity of dioxan for atmospheric moisture proved the most troublesome.

(a) *Ebullioscopic measurements.* Neither water nor dioxan could be used for ebullioscopic measurements with the present compounds. In boiling water, the salts are hydrolysed, giving basic salts, whereas in boiling dioxan partial decomposition to give either dark residues or green colloidal solutions vitiated the determinations. On the other hand, benzene was satisfactory for alkanoates other than the insoluble formate, acetate, and propionate.

Remarkably small elevations in the b. p. of benzene were produced by addition of copper alkanoates, *e.g.*, 1·8 g. of anhydrous copper butyrate in 100 ml. of benzene (0·077M) produced no detectable change (*i.e.*, $<0·002°$) in the temperature of the boiling solvent. Copper laurate and copper stearate (0·03M) also gave extremely small b. p. elevations, corresponding to average molecular complexities of 5·7 and 8·0, respectively. The small number of osmotically active

TABLE 2. *Magnetic data for copper*(II) n-*alkanoates in solution at room temperature.*

Compound	Concn. (M)	t	$10^6\chi_g$	$-10^6\Delta$	$10^6\chi_M$	μ (B.M.)
Aqueous solution.						
$CuSO_4$	0·185	21·2°	9·64	57	1596	1·91
$Cu(H{\cdot}CO_2)_2$	0·582	18·6	9·49	48	1505	1·85
$Cu(CH_3{\cdot}CO_2)_2$	0·226	16·8	8·94	72	1696	1·95
$Cu(C_2H_5{\cdot}CO_2)_2$	0·258	16·6	7·39	96	1646	1·93
$Cu(C_3H_7{\cdot}CO_2)_2$	0·054	18·3	6·03	120	1553	1·87
Benzene solution.						
$Cu(C_3H_7{\cdot}CO_2)_2$	0·022	20·0	3·33	120	912	1·42
$Cu(C_4H_9{\cdot}CO_2)_2$	0·004	20·4	*ca.* 2·8	144	888	*ca.* 1·4
Dioxan solution.						
$Cu(H{\cdot}CO_2)_2$	0·008	18·0	2·89	48	492	1·01
$Cu(CH_3{\cdot}CO_2)_2$	0·028	23·0	4·21	72	837	1·36
$Cu(C_2H_5{\cdot}CO_2)_2$	0·071	15·8	3·05	96	736	1·26
$Cu(C_3H_7{\cdot}CO_2)_2$	0·123	18·1	2·52	120	719	1·25
$Cu(C_4H_9{\cdot}CO_2)_2$	0·012	21·7	2·19	144	726	1·26
$Cu(C_{11}H_{22}{\cdot}CO_2)_2$	0·008	18·8	1·2	280	860	1·37
$Cu(C_{17}H_{35}{\cdot}CO_2)_2$	0·004	18·0	*ca.* 0·5	315	770	*ca.* 1·3

particles in boiling benzene, taken in conjunction with the critical solution behaviour displayed by these alkanoates, indicates the presence of micelles in the boiling solvent. Since it is probable that the degree of dispersion of the copper alkanoates in benzene changes from molecular to micellar at the C.S.T., the ebullioscopic determinations were not further pursued.

The ebulliometer was adapted from the design of Sucharda and Bobranski.[10]

(b) *Cryoscopic measurements.* Cryoscopic determinations of the molecular complexity of copper alkanoates in solution were restricted to lower homologues since the higher members display critical solution phenomena well above the f. p.s of dioxan and of benzene. None of the salts was sufficiently soluble in benzene at its f. p. for measurements to be made. However, measurements were made in water for salts in the range formate to butyrate, and in dioxan for salts in the range acetate to valerate.

Dioxan is not usually regarded as a suitable solvent for cryoscopic work on account of its strongly hygroscopic nature. However, efficacy as a solvent for the present compounds, coupled with a convenient f. p. (*ca.* 12°), made an investigation of its cryoscopic properties most desirable.

The cryoscopic illustrated in Fig. 1 was designed so that measurements could be made in an enclosed moisture-free atmosphere. The stirrer and Beckmann thermometer both pass through a B.45 cone containing mercury which seals the interior of the cryoscope. The solute is contained in two thin-walled bulbs supported on a W-shaped hook. Each bulb can be dropped separately into the solvent by either a clockwise or a counter-clockwise rotation of the supporting B.14 joint; the bulbs are then broken with the stirrer. A drying tube [$Mg(ClO_4)_2$] attached to a second B.14 cone is necessary to prevent mercury in the seal around the stirrer from being sucked into the solvent when the cryoscope is first cooled below room temperature.

B.D.H. dioxan (" Specially Pure ") was dried (Na) and used without further purification. The molar cryoscopic constant, azobenzene being used as calibrating solute, was found to be

[10] Sucharda and Bobranski, *Chem. Ztg.*, 1927, **51**, 568.

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$K_f = 5{\cdot}00°$, a value considerably larger than that recorded for water ($K_f = 1{\cdot}86°$) but close to that for benzene ($K_f = 4{\cdot}90°$). Molecular weights in water and dioxan are listed in Table 3, where n = molecular complexity. In dioxan, copper alkanoates exhibit molecular complexities close to 2, whereas in water values considerably less than unity are obtained.

TABLE 3. *Cryoscopic molecular weights of copper*(II) n-*alkanoates in solution.*

	Aqueous solution.				Dioxan solution.			
		M				M		
Compound	Concn. (M)	Obs.	Calc.	n	Concn. (M)	Obs.	Calc.	n
$CuSO_4$	0·0203	97·8	160	0·61	—	—	—	—
$Cu(H{\cdot}CO_2)_2$ ...	0·040	104	154	0·68	—	—	—	—
$Cu(CH_3{\cdot}CO_2)_2$	0·100	109	182	0·60	0·0142	348	182	1·92
$Cu(C_2H_5{\cdot}CO_2)_2$	0·101	124	210	0·59	0·0284	403	210	1·92
$Cu(C_3H_7{\cdot}CO_2)_2$	0·016	144	238	0·60	0·0358	480	238	2·02
$Cu(C_4H_9{\cdot}CO_2)_2$	—	—	—	—	0·0084	555	266	2·09

Electrical-conductivity Measurements.—The electrical conductivity of copper alkanoates in each solvent was measured at 25·0° by means of a Philips A.C. Wheatstone bridge (type GM4249). The measurements were made at 1000 c./sec., a Philips immersion cell (type GM4221) with platinised electrodes and a cell constant of 1·395 being used.

FIG. 1. *Cryoscope.*

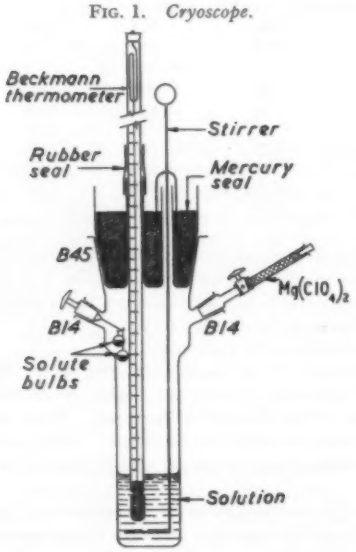
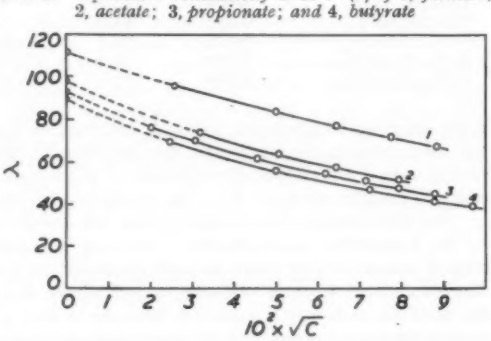


FIG. 2. *Equivalent conductivity at* 25·0° (λ) *of* 1, *formate*; 2, *acetate*; 3, *propionate*; *and* 4, *butyrate*



The dioxan and benzene solutions were non-conductors of electricity within the limits of the equipment, *i.e.*, the specific resistance of the solutions was greater than 10^6 ohms. In contrast, aqueous solutions were good conductors of electricity. The equivalent conductivities for the formate, acetate, propionate, and butyrate, measured in the concentration range 0·01—0·001M, are listed in Table 4 together with the sum of the limiting equivalent conductivities ($\lambda^\circ_{\frac{1}{2}Cu^{++}} + \lambda^\circ_{R.CO_2^-}$) taken from the literature.[11] The variation of equivalent conductivity with square-root of concentration, plotted in Fig. 2, is slightly curved, convex with respect to the concentration axis. This curvature precludes extrapolation of the experimental data to zero concentration. However, for each compound, a smooth extension of the experimental curve can be made which includes the calculated sum of the limiting ionic conductances. The

[11] Robinson and Stokes, "Electrolyte Solutions," Butterworths Scientific Publications, London, 1955, p. 462.

curves for acetate, propionate, and butyrate lie closely parallel to one another, whereas the curve for copper formate decreases slightly less rapidly with increasing values of $\sqrt{C}$.

*Absorption Spectra in Visible and Near Ultraviolet Regions.**—The absorption spectra of copper alkanoates dissolved in water, dioxan and benzene were recorded between 3250 and 8000 Å, a Cary recording spectrophotometer (Model 11 MS-50) being used. The spectra of the laurate, stearate, and behenate both in benzene and in dioxan were recorded above the C.S.T.s' of the compounds. The positions of the absorption bands are listed in Table 5; in addition to

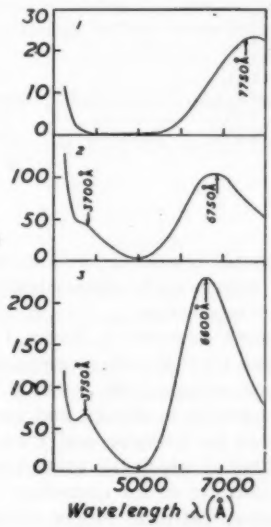


FIG. 3. *Extinction coefficients* (ε) *for copper butyrate in* 1, *water*; 2, *benzene*; 3, *dioxan.*

these, all the solutions absorbed strongly in the ultraviolet region below 3250 Å. Typical spectra are illustrated in Fig. 3.

The spectra of copper butyrate in carbon tetrachloride, chloroform, acetone, and alcohol were also recorded to determine whether the solvent influences either the contour or the position of the 3750 Å band. In carbon tetrachloride this band is as well defined as in dioxan solution

TABLE 4. *Equivalent conductivities of copper*(II) n-*alkanoates in water at* 25·0°

Copper formate								
10^4C (moles l.$^{-1}$)	0	6·707	25·03	41·77	60·00	78·56		
λ (cm.^{2} ohm^{-1} equiv.$^{-1}$) ...	111·2 *	94·7	83·3	76·3	71·1	67·1		
Copper acetate								
10^4C (moles l^{-1})	0	10·21	25·68	41·29	63·00			
λ (cm.^{2} ohm^{-1} equiv.$^{-1}$) ...	97·5 *	73·4	63·6	57·1	51·4			
Copper propionate								
10^4C (moles l.$^{-1}$)	0	4·025	9·354	20·99	38·39	51·26	62·81	77·50
λ (cm.^{2} ohm^{-1} equiv.$^{-1}$) ...	92·4 *	75·9	69·9	61·4	54·1	50·4	47·0	44·3
Copper butyrate								
10^4C (moles l.$^{-1}$)	0	6·146	25·03	52·36	77·32	93·96		
λ (cm.^{2} ohm^{-1} equiv.$^{-1}$) ...	89·2 *	69·4	55·7	46·3	41·1	38·5		

* Calculated sum of limiting equivalent conductivities.

(cf. Fig. 3). On the other hand, in chloroform, acetone, and alcohol, the contour closely resembles that in benzene (cf. Fig. 3), the band being less well defined and apparently displaced slightly (*ca.* 50—80 Å) to shorter wavelengths. A similar effect may be induced in the dioxan

* Extinction coefficients and molarities in this section are based on formula weights.

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spectrum by a rise in temperature; *e.g.*, the definition of the 3750 Å band in dioxan at 70° resembles that in benzene at room temperature.

TABLE 5. *Absorption bands* ($\lambda_{max.}$ *in* Å) *in copper*(II) n-*alkanoate solutions.*

Compound	Solvent: Water	Dioxan	Benzene
$Cu(ClO_4)_2,6H_2O$	*ca.* 8000	insol.	insol.
$Cu(H{\cdot}CO_2)_2$	7750	3750; 6650	insol.
$Cu(CH_3{\cdot}CO_2)_2$	7650	3700; 6650	insol.
$Cu(C_2H_5{\cdot}CO_2)_2$	7650	3750; 6600	insol.
$Cu(C_3H_7{\cdot}CO_2)_2$	7750	3750; 6600	3700; 6750
$Cu(C_4H_9{\cdot}CO_2)_2$	insol.	3750; 6600	3700; 6750
$Cu(C_{11}H_{23}{\cdot}CO_2)_2$	insol.	3600; 6600	3700; 6750
$Cu(C_{17}H_{35}{\cdot}CO_2)_2$	insol.	3700; 6600	3750 *; 6750
$Cu(C_{21}H_{43}{\cdot}CO_2)_2$	insol.	*ca.* 3700; 6550	3750 *; 6750

* Poorly defined.

DISCUSSION

The magnetic, cryoscopic, and spectroscopic behaviour of copper alkanoates in dioxan or benzene convincingly demonstrates that these compounds retain their binuclear configuration in solution.

The magnetic moments in dioxan, 1·31 ± 0·06 B.M. (excluding that of copper formate), and in benzene 1·4 B.M., when compared with the moments in the solid state,[1] 1·38 B.M., and in aqueous solution, 1·90 ± 0·05 B.M., show that the partial quenching in the moment of the solid persists in dioxan and benzene solutions. Intermolecular exchange, of the type suggested by Gilmour and Pink,[3] must be negligible in the concentration range (0·004—0·123M) at which the present measurements were made, and this, in conjunction with the uniformity of the quenching, confirms the presence of intramolecular exchange demagnetisation between copper atoms within the postulated binuclear $Cu_2(R{\cdot}CO_2)_4$ molecules. The jump in moment to 1·90 B.M. in aqueous solution, which is paralleled by a marked colour change from blue-green to blue, demonstrates that the dimeric bridged structure is destroyed by water and that all exchange interactions are effectively removed.

The small additional depression of the moment in dioxan solutions may be significant, in spite of the relatively large experimental scatter of ±0·06 B.M. For example, the moment in dioxan of copper butyrate (the alkanoate most soluble in dioxan and benzene), 1·25 B.M., is *ca.* 0·1 B.M. lower than the moment either in benzene, 1·42 B.M., or in the solid state, 1·37 B.M. That this small lowering may well be real is supported by the consideration that any residual intermolecular exchange forces in the solid would surely be eliminated in solution, and thereby raise the moment in dioxan with respect to that in the solid, as in the case of benzene. It is suggested that this additional depression of 0·1 B.M. in moment, as well as the marked solvating power of dioxan for copper alkanoates, reflects the formation of binuclear $[Cu_2(R{\cdot}CO_2)_4(C_4H_8O_2)_2]$ molecules in this solvent. The presence of dioxan molecules in the two terminal positions [marked " L " in structure (I)] would then appear slightly to enhance $3d_{z^2}$–$3d_{z^2}$ overlap with a concomitant small decrease of 0·1 B.M. in the magnetic moment.

The cryoscopic data in Table 3 further substantiate any conclusions based on the persistence of a binuclear configuration in non-ionising solvents and its disruption in water. In dioxan, the molecular complexities of acetate, propionate, butyrate, and valerate lie in the range 1·9—2·1, amply confirming their dimeric nature in this solvent. The salts are unfortunately too insoluble at the freezing point of benzene for cryoscopic measurements to be made. In aqueous solution molecular complexities in the range 0·6—0·7 indicate rupture of the alkanoate bridges and the presence of a large number of osmotically active particles in solution.

The dioxan and benzene solutions are non-conductors of electricity, a fact equally

consistent with structure (I), structure (II), or the presence of undissociated ion-pairs. Freshly prepared aqueous solutions, on the other hand, are strongly conducting, and equivalent conductivities at a concentration 0·001M are only 20% ± 5% lower than the sum of the ionic conductivities ($\lambda^\circ_{\frac{1}{2}Cu^{++}} + \lambda^\circ_{R\cdot CO_2^-}$) at zero concentration.

The curvature of the λ–$\sqrt{c}$ plot for aqueous copper acetate arises from two competing equilibria involved in the ionic dissociation of this compound. Thus Sircar, Aditya, and Prasad,[12] on the basis of e.m.f. measurements, showed that at concentrations greater than about 0·1M, copper acetate behaves essentially as a fairly strong 1 : 1 electrolyte, whereas at lower concentrations it undergoes feeble dissociation as a 2 : 1 electrolyte. Using a concentration cell of the type

$$Hg|Hg_2(OAc)_2,Cu(OAc)_2(C),HOAc(C_1)||^{Sat.}_{KCl}||HOAc(C_2),Ba(OAc)_2(C),Hg_2(OAc)_2|Hg,$$

and by assuming that barium acetate is totally dissociated, they determined the following equilibrium constants (l. mole^{-1}):

$$Cu(OAc)_2 \rightleftharpoons CuOAc^+ + OAc^- \quad K_1 = 0{\cdot}125\ (30^\circ)$$
$$CuOAc^+ \rightleftharpoons Cu^{++} + OAc^- \quad K_2 = 0{\cdot}004\ (30^\circ)$$

Their conclusions have been fully supported both by conductivity data,[13] which give $K_1 = 0{\cdot}103$ and $K_2 = 0{\cdot}003$ at 0°, and by spectrophometric measurements,[14] which give $K_1 = 0{\cdot}114$ and $K_2 = 0{\cdot}0033$ at 20°.

The present cryoscopic and conductivity data are in harmony with this interpretation. Furthermore, the curvature of the λ–$\sqrt{C}$ plots for formate, propionate, and butyrate so closely match that of the acetate, that it seems probable that the ionic dissociation of these salts should be represented by similar equilibria. The conductivity of these solutions gradually decreases on ageing, and a parallel drop in pH is indicative of slow hydrolysis at room temperature.

The spectroscopic properties of copper alkanoate solutions in the visible and the near ultraviolet region are of particular interest in view of recent single-crystal studies by Tsuchida and Yamada.[5] Most copper(II) complexes usually exhibit not more than one electronic absorption band of moderate intensity in the red or near infrared region, which French and Lowry[15] have termed a "copper band." However, with copper acetate and propionate, in addition to a broad "copper band" at 7000 Å, Tsuchida and Yamada find a new absorption band of a special kind at 3750 Å which they ascribe to the presence of a direct copper–copper linkage. The absorption of this new band is greatly polarised along the copper–copper axis, which is the reverse of the polarisation property of the "copper band" at 7000 Å. Both bands persist in alcohol or chloroform solutions of all alkanoates between acetate and octanoate, as well as in acetic anhydride solutions of palmitate and stearate.

The present spectra of dioxan and benzene solutions also exhibit this ultraviolet band at 3750 Å in addition to a broad "copper band" at 6600 Å in dioxan and 6750 Å in benzene. In contrast, aqueous solutions of copper alkanoates show only one broad absorption band at 7750 Å, which may be compared with the corresponding broad band at *ca.* 8000 Å in aqueous cupric perchlorate. Since the magnetic and cryoscopic properties unambiguously establish the presence of dimeric molecules in dioxan and benzene solutions, Tsuchida and Yamada's suggestion that the 3750 Å band is diagnostic of binuclear copper alkanoate molecules is now completely substantiated.

One of the most interesting results emerging from the present investigations is that copper formate adopts the binuclear configuration when dissolved in dioxan. This is

[12] Sircar, Aditya, and Prasad, *J. Indian Chem. Soc.*, 1953, **30**, 633.
[13] Doucet and Cogniac, *Compt. rend.*, 1955, **240**, 968.
[14] Doucet and Marion, *ibid.*, p. 1616.
[15] French and Lowry, *Proc. Roy. Soc.*, 1924, *A*, **106**, 489.

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proved both by the low moment, $\mu = 1{\cdot}01$ B.M., and the presence of an absorption band at 3750 Å in dioxan solution. Clearly, the donor and non-ionising properties of dioxan induce a complete change from the structure of the solid (a layer structure involving elongated CuO_6 octahedra [16]), and energetically favour formation of discrete binuclear $[Cu_2(H{\cdot}CO_2)_4(C_4H_8O_2)_2]$ molecules. This has been confirmed [17] by isolating from the dioxan solution dichroic blue-green crystals with a magnetic moment $\mu \sim 1$ B.M. These crystals contain dioxan and are readily decomposed in the presence of moisture. In aqueous solution, the magnetic moment jumps from the value 1·64 B.M. of the tetrahydrate to 1·85 B.M., showing that strong intermolecular-exchange interactions are present in the crystalline tetrahydrate. A detailed discussion of the magnetic behaviour of copper formate [17] is deferred.

The critical solution (or Krafft) phenomenon exhibited by the laurate, stearate, and behenate, both in dioxan and in benzene, arises from molecular aggregation in solution, which commences at the C.S.T. The careful measurements by Pink and his co-workers,[7, 8, 18] particularly with zinc alkanoates, provide a sound basis for discussion of the present observations. The slow rise in solubility followed by a sudden and large increase over a very small range in temperature characterises the phenomenon, and, in the present case, is ascribed to a change in the degree of dispersion of the compounds from bimolecular to micellar at this temperature. When cooled below the C.S.T., the alkanoates tend to be precipitated in a very finely divided form. The fact that the heavier alkanoates behave thus even in the presence of a donor solvent like dioxan, together with the observation that the reprecipitated alkanoates contain no dioxan of solvation, indicates that the peripheral hydrocarbon chains are sufficiently long sterically to hinder the terminal positions marked L in structure (I).

The ebullioscopic measurements in benzene show that the average number of molecules per micelle for copper laurate and copper stearate is of the order of 6—8 in 0·03M-solution, whereas for copper butyrate the number must be considerably larger. These values are close to those observed by Pink *et al.* for toluene solutions of the laurate [7] and stearate [8] at a similar concentration. The extremely small number of osmotically active entities in boiling benzene solutions of the butyrate is consistent with their conclusion based on the behaviour of zinc soaps, that the number of molecules per micelle increases with decreasing length of the hydrocarbon chain.

Any detailed discussion concerning the micellar structure would necessarily be speculative at this stage. However, it is clear from the present results that the binuclear molecular structure of copper alkanoates in no way inhibits the formation of micelles, which presumably consist of aggregates of dimeric copper alkanoate molecules. This conclusion is favoured by the persistence of the ultraviolet absorption band at 3750 Å in solutions above the critical temperature. The driving force behind micelle formation is likely to be residual forces of attraction between the peripheral hydrocarbon chains [cf. structure (I)] coupled with weak polar attractions, which presumably are present when the terminal positions, L, are unoccupied. These are shown for example, by the small dipole moment, 1·20 D, observed [19] for copper oleate, which we have recently found to have the binuclear structure.

The authors thank Mr. I. H. Reece for assistance with spectrophotometric measurements and Dr. E. Challen for carbon and hydrogen microanalyses.

Department of Inorganic Chemistry, School of Applied Chemistry,
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[16] Kiriyama, Ibamato, and Matsuo, *Acta Cryst.*, 1954, **7**, 482.
[17] Martin and Waterman, unpublished results.
[18] Tughan and Pink, *J.*, 1951, 1804.
[19] Banerjee and Palit, *J. Indian Chem. Soc.*, 1950, **27**, 385.

280. *The Relative Affinities of an Amine, an Organic Phosphine, and a Sulphide for Cadmium Ion.*

By Sten Ahrland, J. Chatt, N. R. Davies, and A. A. Williams.

The stability constants of the metanilate, 3-sulphotriphenylphosphine, and 4-sulphodiphenyl sulphide ions with cadmium ion have been determined. The first stability constants (K_1) are all smaller than their analogues with silver ion and the difference is very marked in the case of the phosphine. We interpret this great weakening of the phosphine complexes on passing from silver to cadmium to mean that the strength of dative π-bonding from the metal to ligand falls sharply at the end of the transition series of metals.

We [1,2] have already measured the stability constants of a number of similar organic derivatives of nitrogen, phosphorus, arsenic, oxygen, sulphur, and selenium for silver(I) in aqueous solutions and now we describe an extension of that work to cadmium(II) ion. The constants were determined by titrating a solution of cadmium perchlorate with a solution of the ligand, a cadmium amalgam electrode being used to measure the change in concentration of the cadmium ion as the titration proceeded. The experimental method, the method of calculation, and the meanings of the symbols used are given in reference 1.

The cadmium complexes are very weak and their stability constants could not be accurately determined. The greatest change in e.m.f. due to the formation of complexes in any of these experiments was only 13·2 mv. The constants which we have determined are listed in Table 1. It is to be noted that the stabilities of the second complex in the case of the phosphine, and of the third in the case of the sulphide, are enhanced relatively to those of the lower complexes. The accuracy of the determinations is not sufficient to warrant any discussion of the ratios K_1/K_2 except to point out that this ratio in the case of the phosphine appears to be exceptionally low (0·027).

Attempts to obtain the stability constants of the 4-sulphodiphenyl selenide ion failed.

Table 1. *Stepwise stability constants, K (in l. mole^{-1}), and gross stability constants, β, of the ligands, L, with cadmium ion at an ionic strength I and 25°.*

L	I	K_1	K_2	β_2	β_3
3-NH_2·C_6H_4·SO_3^-	1·0	1·8	2	3·5	—
3-PPh_2·C_6H_4·SO_3^-	0·1	≈8	≈300	2500	—
4-SPh·C_6H_4·SO_3^-	0·2	4·7	—	<10	1100

Metal ions which we [1] have designated type (*b*) form their strongest complexes with the second or a subsequent co-ordinating atom rather than with the first from each Group of co-ordinating atoms in the Periodic Table. They probably owe this peculiarity, which distinguishes them from the commoner type (*a*) metal ions, to their ability to release electrons to form dative π-bonds with co-ordinating atoms having suitable orbitals to receive them.[3] The second and subsequent co-ordinating atoms, but not the first, in each Group have vacant *d*-orbitals which can receive electrons to form π-type bonds. The electrons are usually supplied from *d*-orbitals of the metal ion and so class (*b*) character is most marked when the metal ion has filled *d*-orbitals and low ionic charge. Silver(I) has a greater class (*b*) character than any other acceptor ion or molecule, the stabilities of whose complexes with a large range of co-ordinating atoms have been investigated quantitatively.[2] Cadmium(II) is isoelectronic with silver(I), but its ionic charge is twice as great. We should therefore expect the electrons in cadmium(II) to be more strongly held, and particularly its *d*-electrons will not be so readily available for dative π-bonding. Thus the type (*b*) character of cadmium(II) should be less than that of silver(I).

[1] Ahrland, Chatt, Davies, and Williams, *J.*, 1958, 264.
[2] *Idem*, *J.*, 1958, 276.
[3] Chatt, *Nature*, 1950, **165**, 637; Craig, Maccoll, Nyholm, Orgel, and Sutton, *J.*, 1954, **332**; Jaffe, *J. Phys. Chem.*, 1954, **58**, 185.

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Our measurements confirm this view. In Table 2 the first stability constants, K_1, of a representative selection of unidentate ligands with silver(I) and cadmium(II) are given for comparison. Cadmium is evidently near the border between classes (*a*) and (*b*). Its first constants, K_1, with all except the acetate and the fluoride ion, are lower than in the silver series. Those of the amine, sulphide, chloride, and bromide, where we consider dative π-bonding to be absent or weak, even with silver(I), are reduced only by a factor of 10—100 in passing from silver(I) to cadmium(II). On the other hand, the stability constants, K_1, of the phosphine and iodide ion, where d_π-bonding with silver ion is very strong,[2] are reduced by factors of about 10^6. It is evident that the capacity of the metal ions to form strong dative π-bonds falls sharply at the end of the transition series of metals.

Two causes can be advanced for the exceptional behaviour of the acetate and the fluoride ion: (*a*) that the M–O and M–F bonds are largely electrostatic in character and so the anionic ligand is held more strongly by the bipositive cadmium ion than by the isoelectronic but unipositive silver ion; (*b*) that the lone-pair repulsion between the filled d_{xy}-type of orbitals in the metal ion and filled *p*-orbitals of the oygen and fluorine atoms is greater with silver(I) than with cadmium(II) where the greater nuclear charge will contract the *d*-orbitals. Doubtless both of these effects operate, and perhaps entropy effects as well.

TABLE 2. *The first stability constants* K_1(Ag) *and* K_1(Cd) *for a selection of unidentate ligands with silver and cadmium ions at ionic strength I* ($NaClO_4$) *and 25°.**

Ligand	*I*	log K_1(Ag)	*I*	log K_1(Cd)	Ligand	*I*	log K_1(Ag)	*I*	log K_1(Cd)
NH_3	2·0	3·20[a]	2	2·65[a]	F^-	1·0	−0·32[c]	1·0	0·46[f]
3-$NH_2{\cdot}C_6H_4{\cdot}SO_3^-$	1·0	1·23[b]	1·0	0·26[d]	Cl^-	5	3·08[g]	3	1·59[h]
3-$PPh_2{\cdot}C_6H_4{\cdot}SO_3^-$	0·1	8·15[b]	0·1	~0·9[d]	Br^-	0	4·38[i]	0	2·23[j]
$CH_3{\cdot}CO_2^-$	3·0	0·37[l]	3·0	1·30[l]				3	1·76[h]
4-$SPh{\cdot}C_6H_4{\cdot}SO_3^-$ ...	0·2	1·67[c]	0·2	0·67[d]	I^-	4	8·13[k]	3	2·08[h]

* Many determinations of the constants for the halide ions are available in the literature. These were chosen as giving the best comparison between silver and cadmium. Vertical comparisons are not so good because of differences in ionic strength.

[a] At 30° in NH_4NO_3; J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," Haase and Son, Copenhagen, 1941, pp. 134, 160. [b] Ref. 2. [c] Ref. 1. [d] This work. [e] Leden and Marthén, *Acta Chem. Scand.*, 1952, **6**, 1125. [f] Ref. 4, p. 49. [g] Leden, *Svensk kem. Tidskr.*, 1953, **65**, 88. [h] Leden, *Z. phys. Chem.*, 1941, *A*, **188**, 160. [i] Berne and Leden, *Z. Naturforsch.*, 1953, **8**, *a*, 719. [j] Kivalo and Ekari, *Suomen Kem.*, 1957, *B*, **30**, 116. [k] Leden and Parck, *Acta Chem. Scand.*, 1956, **10**, 535; Leden, *ibid.*, p. 812. [l] At 20°; Leden, *Svensk kem. Tidskr.*, 1946, **58**, 129; see also ref. 4, p. 89.

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The preparations of the sulphonated ligands used in these investigations have been described.[1,3] The constants were determined by the same method as those of the sulphonated amines, sulphide, and selenide with silver ion.[1] Cadmium amalgam (10%) electrodes were used in place of the Ag–AgCl electrodes, and cadmium perchlorate in place of silver perchlorate. The cell in which the measurements were made was similar to that used in the silver experiments, but the amalgam electrode half-cell had two small pockets in the base connected by sealed-in platinum contacts to the outer circuits, and two manually operated platinum-wire stirrers through the top of the cell and capable of reaching into the pockets. The pockets were used to contain the amalgam (½—1 c.c.), and the stirrers to clean its surface whenever contamination was suspected. The amalgam was prepared and used as described by Leden.[4] The e.m.f.s of the cells were very stable and reproducible to 0·2—0·3 mv.

The experimental results are given in Tables 3—5. C_L' is the concentration of ligand solution used to titrate the cadmium perchlorate solution of ionic strength *I* ($NaClO_4$). C_L is the actual concentration of ligand in the half-cell, and E_M the change in e.m.f. of the cell caused by complex formation between the ligand and cadmium ion. X, X_1, etc., are functions defined in the appendix to reference 1. In all the experiments complex formation was so weak that E_M was virtually independent of the initial concentration of cadmium ion C_M' at the concentrations used.

[4] Leden, "Potentiometrisk Undersöking av Några Kadmiumsalters Komplexitet," Gleerupska Univ.-Bokhandeln, Lund, 1943, p. 34.

Sodium Metanilate.—Titrations were performed at $C_M' = 20$ mM and 5 mM. Complex formation was so weak that even at $C_L = 500$ mM the ligand number $\bar{n}$ did not exceed 1·5 (Table 3).

TABLE 3. *The system cadmium ion–metanilate ion.*

($C_L' = 1$M; $I = 1$M)

$C_L = [L]$	E_M	X	X_1	X_2	$C_L = [L]$	E_M	X	X_1	X_2
38·5	0·9	1·072	1·9	—	285·7	7·5	1·790	2·77	3·4
62·5	1·5	1·125	2·0	—	318	8·3	1·908	2·86	3·3
90·9	2·3	1·195	2·14	—	348	9·2	2·048	3·01	3·5
117·6	3·0	1·265	2·26	—	400	10·6	2·285	3·22	3·6
166·7	4·3	1·398	2·39	3·5	444	11·7	2·490	3·36	3·5
210·5	5·5	1·534	2·54	3·5	500	13·2	2·798	3·60	3·6
250·0	6·5	1·658	2·63	3·3					

$\beta_1 = K_1 = 1·8 \pm 0·2$ l. mole^{-1}; $\beta_2 = 3·5 \pm 0·2$ l.^{2} mole^{-2}; $K_2 = 2$ l. mole^{-1}.

Sodium Salt of 3-Sulphotriphenylphosphine.—This ligand caused a precipitate at $C_M' > 2$ mM. Titrations were therefore performed at $C_M' = 1$ and $C_M' = 0·5$ mM. The use of these low concentrations set the limits to the accuracy of the experiment (Table 4).

TABLE 4. *The system cadmium ion–3-sulphotriphenylphosphine ion.*

($C_L' = 0·03$M; $I = 0·1$M)

$C_L = [L]$	E_M	X	X_1	X_2	$C_L = [L]$	E_M	X	X_1	X_2
1·88	0·5	1·040	21	—	9·57	3·1	1·273	28·5	2100
3·54	0·6	1·048	14	—	10·44	3·5	1·312	29·9	2100
5·01	0·8	1·064	13	—	12·00	5·0	1·476	39·6	2600
6·33	1·0	1·081	13	—	13·32	5·8	1·570	42·8	2600
7·50	1·7	1·141	18·8	—	15·00	6·9	1·710	47·3	2600
8·58	2·2	1·187	21·8	—					

$\beta_1 = K_1 \approx 8$ l. mole^{-1}; $\beta_2 = 2500$ l.^{2} mole^{-2}; $K_2 \approx 300$ l. mole^{-1}.

Sodium Salt of 4-Sulphodiphenyl Sulphide.—Titrations were performed at $C_M' = 20$, 10, and 5 mM (Table 5).

TABLE 5. *The system cadmium ion–4-sulphodiphenyl sulphide ion.*

($C_L' = 0·2$M; $I = 0·2$M)

$C_L = [L]$	E_M	X	X_1	X_2	X_3	$C_L = [L]$	E_M	X	X_1	X_2	X_3
7·69	0·5	1·040	5·2	—	—	57·1	4·8	1·453	7·9	56	980
12·50	0·8	1·064	5·1	—	—	63·6	5·8	1·570	9·0	68	1070
18·2	1·2	1·098	5·4	—	—	69·6	6·9	1·710	10·2	79	1130
23·5	1·6	1·134	5·7	—	—	80·0	8·7	1·968	12·1	93	1160
33·3	2·3	1·195	5·9	36	1100	88·9	10·3	2·231	13·8	100	1120
42·1	3·1	1·273	6·5	43	1020	100·0	12·3	2·608	16·1	114	1140
50·0	3·9	1·355	7·1	48	960						

$\beta_1 = K_1 = 4·7 \pm 0·5$ l. mole^{-1}; $\beta_2 < 10$ l.^{2} mole^{-2}; $\beta_3 = 1100 \pm 200$ l.^{3} mole^{-3}.

Sodium Salt of 4-Sulphodiphenyl Selenide.—Steady cell potentials were not obtained with this ligand. It appeared to attack the surface of the amalgam electrode because stirring the amalgam caused a change in potential of 0·25 mv, and without stirring the potentials fluctuated irregularly. No constants were obtained.

The authors are greatly indebted to Dr. I. Leden for useful discussion.

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
AKERS RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS.

[*Received, November 14th*, 1957.]

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281. *Heats of Combustion and Molecular Structure. Part V.*[1] *The Mean Bond Energy Term for the* C–O *Bond in Ethers, and the Structures of Some Cyclic Ethers.*

By R. C. Cass, S. E. Fletcher, C. T. Mortimer, H. D. Springall, and T. R. White.

The mean bond energy term for the C–O bond in ethers has been reconsidered in conjunction with combustion data on tetrahydropyran and used in a molecular structural analysis of combustion data on cyclic ethers and on diphenyl ether.

A suitable starting point for the study, by combustion, of the molecular energetics of organic compounds containing carbon, hydrogen, and oxygen appeared to be the mean bond energy term, $\overline{E}$(C–O), in ethers. By studying combustion data on simple ethers and obtaining experimental results for tetrahydropyran we obtained a reasonable value, and applied it to the molecular structural analysis of the experimentally determined heats of combustion of the cyclic ethers dihydropyran, tetrahydrofuran, dibenzopyran, and dibenzofuran, and of diphenyl ether.

Experimental

Preparation and Purification of Materials.—Some microanalyses are by Mr. W. Morton (University of Manchester).

Benzoic acid. B.D.H. Thermochemical Standard was used.

Tetrahydropyran (Kodak Ltd.) was refluxed over sodium and distilled, the fraction, b. p. 86·9—87·1°/744 mm. (Clark [2] gives b. p. 88·0°/760 mm.) being used for combustion ($n_D^{19·6}$ 1·4198; Skuratov [3] gives n_D^{20} 1·4212 and Heilbron and Bunbury [4] give $n_D^{18·5}$ 1·4195) (Found: C, 69·86; H, 11·66. Calc. for $C_5H_{10}O$: C, 69·72; H, 11·70%).

Dihydropyran (I.C.I.) was partially dried with anhydrous sodium carbonate, then fractionated, the fraction, b. p. 84—85°, being collected. It was dried by prolonged refluxing with sodium until it no longer evolved hydrogen when brought into contact with a freshly prepared sodium surface (for the difficulty of drying dihydropyran, see Sawyer and Andrus [5]). Most of the dihydropyran so dried distilled at 84·4°/742 mm. (Sawyer and Andrus [5] give 84—86°) (Found: C, 71·4; H, 9·5. Calc. for C_5H_8O: C, 71·4; H, 9·5%).

Tetrahydrofuran (I.C.I.) was dried (CaH_2) and fractionated from phosphoric oxide through a Fenske column. The product, b. p. 64·0—66·2°, was collected, refluxed over sodium for 1 hr., and again fractionated. It distilled almost completely at 66·0°/768 mm. (Starr and Hixon [6] give b. p. 64—66°/760 mm.) (Found: C, 66·5; H, 10·9. Calc. for C_4H_8O: C, 66·7; H, 11·1%).

Diphenyl ether (British Scherring Research Institute) was twice recrystallised from 90% ethanol and was further purified by fractional freezing twice, by the method described by Schwab and Wichers [7] for the purification of benzoic acid. The product, m. p. 27·2° (Timmermans [8] gives 26·9°) was powdered in an agate mortar and stored over phosphoric oxide.

Dibenzopyran (L. Light and Co., Ltd.) was recrystallised four times from 95% ethanol, m. p. 100·4—100·5° (Ipatiev, Orlov, and Petrov [9] give m. p. 100·5°).

[1] Part IV, Cass, Fletcher, Mortimer, Quincey, and Springall, *J.*, 1958, 958.
[2] Clarke, *J.*, 1912, **101**, 1802.
[3] Skuratov, Moscow University, personal communication.
[4] Heilbron and Bunbury, "Dictionary of Organic Compounds," Eyre and Spottiswoode, London, 1946.
[5] Sawyer and Andrus, *Organic Syntheses*, Coll. Vol. **3**, p. 276.
[6] Starr and Hixon, *Organic Syntheses*, Coll. vol., **2**, p. 566.
[7] Schwab and Wichers, *J. Res. Nat. Bur. Stand.*, 1940, **25**, 747.
[8] Timmermans, "Physico-chemical Constants of Pure Organic Compounds," Elsevier, Brussels, 1950.
[9] Ipatiev, Orlov, and Petrov, *Ber.*, 1927, **60**, 130.

Dibenzofuran (L. Light and Co., Ltd.) was dissolved in ether and shaken with two successive portions of aqueous sodium hydroxide (2M). The ether solution was then washed with water, separated, and dried ($MgSO_4$). The solvent was evaporated off and the dibenzofuran was twice recrystallised from 80% ethanol and dried *in vacuo*. The colourless product had m. p. 81·9—82° (Cullinane and Plummer [10] give m. p. 82·4°) (Found: C, 85·8; H, 4·8. Calc. for $C_{12}H_8O$: C, 85·7; H, 4·8%).

Vapour-pressure Measurements.—Accurate vapour-pressure data were available only for diphenyl ether and tetrahydrofuran. The vapour pressures of the other compounds were measured in an apparatus of the type described by Sanderson.[11] The values of A and B of the equation $\log_{10}p$ (mm.) $= A/T + B$ are given in Table 1, together with those for the two compounds previously investigated. The derived latent heats of vaporisation (liquid to vapour), given by $L_v = -4{\cdot}56A \times 10^{-3}$ kcal./mole, are also listed.

TABLE 1. *Latent heats.**

Compound	$-A$	B	Temp. range	L_v (kcal./mole)
Tetrahydropyran	1825·35	7·99	0—15°	8·35
Dihydropyran	1680·98	7·57	0—15	7·7
Tetrahydrofuran [a]	1660·5	7·80	20—60	7·6
Diphenyl ether [b]	3351·9	9·58	40—60	15·2
Dibenzopyran	4632·4	11·58	140—160	21·2
Dibenzofuran	3457·6	9·38	130—145	15·8

* For compounds burnt as solids, the latent heat of fusion was assumed to be 4 kcal./mole (Walden, *Z. Elektrochem.*, 1908, **14**, 713) and is added to the L_v term to give the latent heat of sublimation, L_s^{25}.
[a] Klages and Mohler, *Ber.*, 1948, **81**, 411. [b] Bent and Francel, *J. Amer. Chem. Soc.*, 1948, **70**, 634.

TABLE 2. *Tetrahydropyran* (M, 86·13).

Wt. taken,* m (g.)	CO_2 (obs. : calc.)	ΔR (ohms)	Corrections (cal.) (fuse)	(HNO_3)	(carbon)	C (cal./ohm)	$-\Delta U_b$ † (kcal./mole)
0·2699	1·0010	0·06088	24·9	0·7	—	2·8	751·6
0·3954	1·0009	0·08892	24·1	1·3	—	4·1	751·1
0·4208	1·0020	0·09468	17·2	1·0	—	4·4	751·0
0·3320	1·0012	0·07472	22·8	1·4	7·8	3·5	752·9

* Weight *in vacuo*.
† $-\Delta U_b = 10^{-3}\ M/m\ [(E + C)\Delta R - \text{Corr. (fuse} + HNO_3 - \text{carbon)}]$ kcal./mole.

Combustion Calorimetry.—Tetrahydropyran was burnt in a twin-valve Parr bomb (energy equivalent, $E = 39{,}058 \pm 20$ cal./ohm) as described in Part IV.[1] The results are given in Tables 2 and 4. In only one case was carbon found in the bomb after combustion. It was weighed and a correction of 7·84 kcal./g. was applied. The carbon dioxide formed on combustion varied from the calculated quantity to 0·20% above it (the experimental error of analysis is approximately ±0·05%), probably owing to very slight contamination by dihydropyran from which the tetrahydropyran was prepared, the b. p.s of the two compounds being being only 3° apart. (The high carbon and low hydrogen contents found in the microanalysis of tetrahydropyran are compatible with this.) The experimental error ascribed to $-\Delta U_b$ and $-\Delta H_c°$ of ±0·9 kcal./mole has been increased to ±1·5 kcal./mole to include the uncertainty due to the slight impurity.

The $-\Delta U_b$ terms were converted into $-\Delta H_c°$ terms, the standard heat of combustion, by use of the expression

$$-\Delta H_c° = -\Delta U_b - w - \Delta nRT,$$

where w is the Washburn correction, calculated according to Prosen,[12] and Δn is the increase in the number of molecules of gas in the combustion reaction.

Slightly lower values of $-\Delta H_c°$ for tetrahydropyran have been reported by Dr. G. R. Nicholson (Imperial Chemical Industries Limited, Blackley), 749·0 kcal./mole,[13] and Professor

[10] Cullinane and Plummer, *J.*, 1938, 63.
[11] Sanderson, "Vacuum Manipulation of Volatile Compounds," Wiley, New York, 1948, p. 48.
[12] Prosen, "Experimental Thermochemistry," ed. Rossini, Interscience, New York, 1956.
[13] Nicholson, personal communication.

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S. M. Skuratov and his co-workers (Moscow), 750·1 ± 0·2 kcal./mole.[14] We thank Dr. Nicholson and Professor Skuratov for discussions which lead us to feel that any significant discrepancies between their values and ours are probably due to undetected contamination of their specimens by dihydropyran.

The remaining combustions were made in a Mahler-Cook stainless-steel bomb. The energy equivalent of the calorimeter system, E', was $3085{\cdot}5 + 24{\cdot}18\theta_m$ cal./deg., where θ_m is a mean temperature, as defined in Part I.[15] The apparatus, experimental procedure, and method of calculation were fully described in Part I.[15] Diphenyl ether, dibenzofuran, and dibenzopyran were burnt as solids, and the remainder as liquids in glass ampoules. The results are recorded in Tables 3 and 4.

TABLE 3.

Wt. taken, m (g.) *	$\Delta\theta$ (° c)	θ_m (° c)	Corrections (cal.) (fuse)	(HNO_3)	(carbon)	E' (cal./deg.)	C (cal./deg.)	$-\Delta U_b$ † (kcal./mole)
			Dihydropyran (M, 84·11)					
0·7907	2·0950	4·69	71·8	2·2	0·8	3198·0	0·7	705·6
0·8252	2·1847	4·65	71·8	2·5	3·2	3197·0	0·7	705·3
0·9749	2·5624	4·78	31·9	2·8	1·6	3200·5	0·8	705·3
0·9080	2·3885	4·53	31·9	2·8	3·9	3195·0	0·8	704·8
0·8336	2·2083	4·61	71·8	2·7	2·2	3196·5	0·8	705·6
			Tetrahydrofuran (M, 72·10)					
0·8654	2·2785	4·22	71·8	1·7	4·8	3187·0	0·8	599·4
0·9716	2·5359	4·66	71·8	2·4	5·2	3198·0	1·0	596·9
0·9771	2·5569	4·57	71·8	3·1	3·6	3196·0	1·0	597·9
0·9906	2·5999	4·26	71·8	2·9	6·4	3188·0	1·0	598·5
			Diphenyl ether (M, 170·20)					
0·7974	2·1391	4·75	4·0	1·8	1·6	3199·0	0·5	1459·9
0·8126	2·1813	4·68	4·0	0·8	0·8	3197·5	0·5	1460·2
0·8036	2·1644	4·36	4·0	0·7	3·9	3190·5	0·5	1462·6
			Dibenzopyran (M, 182·21)					
0·8612	2·3133	4·44	71·8	2·8	1·6	3192·0	0·5	1547·0
0·8724	2·3439	4·52	71·8	3·0	0·8	3194·0	0·5	1548·4
0·8937	2·4013	4·56	71·8	2·0	1·2	3195·0	0·5	1549·6
0·8979	2·4150	4·46	71·8	2·2	2·4	3192·5	0·5	1550·2
			Dibenzofuran (M, 168·18)					
0·8223	2·1717	4·31	71·8	1·1	2·3	3189·0	0·4	1402·2
0·8826	2·3240	4·31	71·8	1·7	1·9	3189·0	0·5	1398·8
0·9040	2·3784	4·62	71·8	2·2	1·6	3196·0	0·5	1400·9

* Weight *in vacuo*.
† Where $-\Delta U_b = 10^{-3}\, M/m\, [(E' + C)\, \Delta\theta - \text{corr. (fuse} + HNO_3 - \text{carbon})]$ kcal./mole.
For symbols see Part I.[15]

TABLE 4.

Compound	$-\Delta U_b$ mean (kcal./mole)	Standard deviation ($-\Delta U_b$) (%)	Overall standard deviation (%)	Washburn corrn., w (kcal./mole)	ΔnRT (kcal./mole)	$\Delta H_c°$ (kcal./mole)
Tetrahydropyran ...	751·9	0·120	0·160	0·30	−1·2	752·8 ± 1·5
Dihydropyran	705·3	0·020	0·032	0·35	−0·9	705·9 ± 0·3
Tetrahydrofuran	598·2	0·085	0·089	0·26	−0·9	598·8 ± 0·5
Diphenyl ether	1460·9	0·058	0·063	0·95	−1·2	1461·1 ± 0·9
Dibenzopyran	1548·8	0·045	0·052	1·05	−1·2	1549·0 ± 0·9
Dibenzofuran	1400·6	0·062	0·067	1·0	−0·9	1400·5 ± 1·0

DISCUSSION

Derivation of the Mean Bond Energy Term $\bar{E}$(C–O) *in Ethers.*—The only available experimental data on the heats of combustion of simple ethers were found in the classical work of Berthelot and of Thomsen (*circa.* 1890) and are considered in the compilations of Kharasch [16]

[14] Skuratov, Kozina, Shteher, and Varushyenko, I.U.P.A.C. Thermochemical Bulletin, 1957, No. 3.
[15] Springall, White, and Cass, *Trans. Faraday Soc.*, 1954, **50**, 815.
[16] Kharasch, *J. Res. Nat. Bur. Stand.*, 1929, **2**, 359.

and, to some extent, of Bichowsky and Rossini.[17] The three simplest ethers, dimethyl,[18] ethyl methyl,[18] and diethyl,[19] were investigated in the gas phase by flame calorimetry. The heats of combustion found, listed in Table 5, have been the basis of all previous estimates of $\bar{E}$(C–O) in ethers (*e.g.*, Pauling [20]), special weight being attached to the data on dimethyl ether.* These data have been analysed afresh by use of the methods and auxillary thermochemical data (heats of formation of carbon dioxide and water, heats of atomisation of elements, and other mean bond energy terms) discussed in earlier Parts [1, 15, 21, 22] [$-\Delta H_f°$ terms: CO_2, 94·05, H_2O, 68·32. ΔH_a terms: C, 171·7; H, 52·09; O, 58·98. $\bar{E}$(b) terms: C–C, 83·1; C–H, 98·85 kcal./mole]. The derived heats of formation of the gaseous compounds, $-\Delta H_{f,g}{}^{st}$, atomic heats of formation, $-\Delta H_{f,g}{}^{a}$, and individual $\bar{E}$(C–O) terms are given in Table 5.

We felt it desirable to have an experimental link between this classical work and our own and therefore selected tetrahydropyran as a suitable ether for a new determination. This compound is reasonably accessible, not unduly volatile, and has a structure unlikely to be complicated by strain (see, for example, the dipole-moment studies of H. de Vries Robles [23]). $-\Delta H_{c,g}$ for this compound, and the derived $-\Delta H_{f,g}$ $-\Delta H_{f,g}{}^{a}$, and $\bar{E}$(C–O) terms are listed in Table 5.

TABLE 5.

(Energy terms in kcal./mole)

Compound	$-\Delta H_{c,g}$	$-\Delta H_{,g}{}^{st}$	$-\Delta H_{f,g}{}^{a}$	$\bar{E}$(C–O)
Dimethyl ether	347·6	45·5	760·5	83·9
Ethyl methyl ether	503·4	52·1	1043·0	84·6
Diethyl ether	660·4	57·7	1324·5	84·8
Tetrahydropyran	761·2 *	50·7	1489·2	84·2

* Given by $-\Delta H_{c,g} = -\Delta H_c° + L_v$.

The agreement between the values $\bar{E}$(C–O) derived from the classical data and from our own work is gratifying and seems to justify the use of the average of these four estimations, 84·3 kcal./mole, as a reasonable value for $\bar{E}$(C–O) in ethers [Coates and Sutton [24] have established $\bar{E}$(C–O) in alcohols as 85·5 kcal./mole].

Molecular Energetics of the Cyclic Ethers and of Diphenyl Ether.—The previous approach [15] was followed. For each compound the following calculations were made. (i) $-\Delta H_{f,g}{}^{a}$ was evaluated from the experimental $-\Delta H_c°$ and $L_g{}^{st}$ or L_v terms. (ii) The mean bond energy terms for all the bonds in the molecule were summed, $\sum \bar{E}$(b). (iii) The difference $-\Delta H_{f,a} - \sum \bar{E}(b) = \Delta E$ was evaluated. This quantity, ΔE, indicates molecular stabilisation when positive; molecular strain when negative. These data are given in Table 6.

TABLE 6.

(Energy terms in kcal./mole)

Compound	$-\Delta H_{f,g}{}^{a}$	$\sum \bar{E}$(b)	ΔE	Compound	$-\Delta H_{f,g}{}^{a}$	$\sum \bar{E}$(b)	ΔE
Dihydropyran	1364·4	1356·9	7·5	Diphenyl ether	2628·4	2544·9	83·5
Tetrahydrofuran	1205·8	1208·7	−2·9	Dibenzopyran	2802·3	2711·1	91·2
				Dibenzofuran	2517·9	2430·3	87·6

Dihydropyran (I) shows a stabilisation energy of 7·5 kcal./mole, probably owing to resonance involving the ionic form (II).

Tetrahydrofuran shows a destabilisation (strain) energy of 2·9 kcal./mole, whereas the strain energy of *cyclo*pentane is about 6 kcal./mole. In the latter case, where the bond angles

* Possibly because the Bichowsky–Rossini compilation only deals with organic compounds up to C_8.

[17] Bichowski and Rossini, "The Thermochemistry of the Chemical Substances," Reinhold, New York, 1936.
[18] Thomsen, "Systematische durchsührung Thermochemischer Untersuchungen," Enke, Stuttgart, 1906, p. 343.
[19] Stohmann, *J. prakt. Chem.*, 1887, **35**, 40, 136.
[20] Pauling, "The Nature of the Chemical Bond," Oxford Univ. Press, 1950.
[21] Cass, Springall, and Quincey, *J.*, 1955, 1188.
[22] Springall and White, *J.*, 1954, 2764.
[23] H. de Vries Robles, *Rec. Trav. chim.*, 1940, **59**, 184.
[24] Coates and Sutton, *J.*, 1948, 1187.

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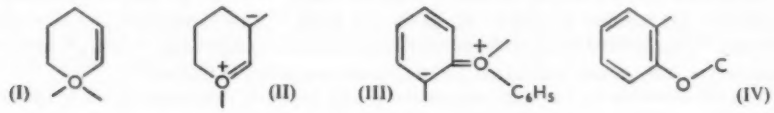
are almost equal to the normal tetrahedral angle, the strain is attributed to small repulsive forces between hydrogen atoms on adjacent carbon atoms.[20] A strain energy slightly less than that of *cyclo*pentane is, therefore, to be expected for tetrahydrofuran, owing to the separation of two of the methylene groups by an oxygen atom. The planar model of tetrahydrofuran constructed from electron-diffraction data [25] (C–C, 1·34; C–O, 1·43 Å; C–O–C = 111° ± 2°) shows only slight strain in the C–C–C angles. For the C–O–C angles, a value of



100° has been allotted by Brie [26]. From electron-diffraction data, Sutton and Brockway [27] give a value of 111° ± 4° for this angle in dimethyl ether. We now suggest a value of 105° ± 5° for the C–O–C angle in dihydropyran.

Diphenyl ether has a stabilisation (resonance) energy of 83·5 kcal./mole. The value 41·8 kcal. for the fragment C_6H_5–O is in good agreement with the value 41·6 kcal./C_6H_5–O fragment which can be derived from the reported heats of combustion of methyl phenyl ether and ethyl phenyl ether.[28] There is an increase of 2·7 kcal. in the resonance energy for the C_6H_5–O fragment above that of the C_6H_5–C fragment taken as about 38·9 kcal. Moreover, (*a*) the C–O–C angle in aromatic ethers (125° ± 5°) is larger than that [29] in aliphatic ethers (105° ± 5°) and (*b*) the C–O distance in aromatic ethers (1·36 Å) is shorter than that [30] in aliphatic ethers (1·42 Å). These facts all agree with the suggestion [31] of the occurrence of resonance of the type (III).

Dibenzopyran and dibenzofuran have resonance energies of 91·2 and 87·6 kcal./mole respectively (45·6 and 43·8 kcal./mole for half of the molecule in each compound) compared with 83·5 kcal./mole in diphenyl ether. The stabilisation of the dibenzopyran relative to diphenyl ether, 7·7 kcal., is probably real and may well be due to the increase in molecular rigidity, relative to diphenyl ether, due to the 2 : 2′-methylene bridge, coupled with the angular conditions in the pyran ring system which favour a C–O–C angle of 125°. The whole molecule may be planar, since folding of the molecule along the CH_2–O axis would introduce angular strain particularly at the oxygen atom and also depress the resonance effect, because of the non-planar system (IV) involved. The intermediate position of dibenzofuran is probably due to the fact that though the molecule is constrained to a planar configuration (as suggested by Cullinane and Plummer [10] and Cullinane and Rees [32]) so stabilising the ionic oxonium forms, nevertheless the bond angles in the furan section are strained; the C–O–C angle, in particular, is likely to be smaller than 125°.

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[25] Beach, *J. Chem. Phys.*, 1941, **9**, 54.
[26] Brie, *Anales Soc. españ. fis. quim.*, 1932, **30**, 483.
[27] Sutton and Brockway, *J. Amer. Chem. Soc.*, 1935, **57**, 473.
[28] Badoche, *Bull. Soc. chim. France*, 1941, **8**, 212; May and Springall, unpublished results.
[29] Smyth and Walls, *J. Amer. Chem. Soc.*, 1932, **54**, 3230; Maxwell, Hendricks, and Mosely, *J. Chem. Phys.*, 1935, **3**, 699; Coop and Sutton, *J.*, 1938, 1869; Plieth, *Z. Naturforsch.*, 1947, **20**, 409; Leonard and Sutton, *J. Amer. Chem. Soc.*, 1948, **70**, 1564.
[30] Hassel and Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149.
[31] Sutton and Hampson, *Trans. Faraday Soc.*, 1935, **31**, 945.
[32] Cullinane and Rees, *Trans. Faraday Soc.*, 1940, **36**, 507.

282. 5-*Alkylacridines. Part II.*[1] *Dialkylaminoalkylacridines.*

By N. Fisher, C. S. Franklin, E. N. Morgan, and D. J. Tivey.

A series of 5-dialkylaminoalkylacridines has been prepared, *viz.* R·$[CH_2]_n$·NR'_2 where R = 5-acridinyl, n = 1—4, R′ = Me or Et, together with certain corresponding mono- and di-quaternary compounds. Hofmann degradation of 5-acridinylmethyltrimethylammonium iodide gave 5-vinylacridine.

The availability[1] of the reactive 5-methylacridine prompted further work on 5-ω-dialkylaminoalkylacridines as potential chemotherapeutic agents.

5-Bromomethylacridine with dimethyl- and diethyl-amine gave the corresponding 5-dialkylaminomethylacridines. The dimethylamino-compound so formed with dimethyl sulphate at room temperature furnished 5-acridinylmethyltrimethylammonium monomethosulphate, and this on further treatment with dimethyl sulphate, at 90°, gave the dimethosulphate. The monoquaternary bromides of 5-dimethylaminomethyl- and 5-diethylaminomethyl-acridine were obtained directly on treatment of 5-bromomethylacridine with trimethyl- and triethyl-amine respectively.

5-Methylacridine, formaldehyde, and dimethylamine under normal Mannich conditions gave the known 5-(2-dimethylaminoethyl)acridine.[2] In a comparable manner, the 5-(2-dimethylaminoethyl) analogues of 3-chloro- and 2-chloro-7-methoxy-acridine were prepared. Stepwise quaternisation of the first of these three products was achieved, as above, by treatment with dimethyl sulphate.

Hofmann degradation of the monomethiodide or monomethosulphate of the 5-(2-dimethylaminoethyl)acridine gave 5-vinylacridine. A boiling dilute solution of the latter in 2N-hydrochloric acid was transformed into a clear yellow polymer on cooling. Catalytic reduction of 5-vinylacridine gave the known 5-ethylacridine.[3]

Methyl β-5-acridinylpropionate was reduced by lithium aluminium hydride to 3-5′-acridanylpropan-1-ol, which on oxidation by ferric chloride furnished 3-5′-acridinylpropan-1-ol. The latter alcohol with hydrobromic acid gave 3-5′-acridinylpropyl bromide and thence by treatment with dimethylamine 5-(3-dimethylaminopropyl)acridine. The 3-chloroacridine analogues were also prepared. Mono- and di-methosulphates of 5-(3-dimethylaminopropyl)acridine were obtained as in the previous cases.

5-(2-Hydroxyethyl)acridine was converted by thionyl chloride into the chloroethyl compound, converted by the malonic ester synthesis into γ-5-acridinylbutyric acid. In a manner comparable with that described above, the derived methyl ester was converted into 5-(4-dimethylaminobutyl)acridine, whose mono- and di-methosulphate were also prepared.

Experimental

5-Dimethylaminomethylacridine Dihydrochloride.—5-Bromomethylacridine (3·5 g.) in benzene (150 c.c.) was refluxed while dry dimethylamine was slowly bubbled through it (2 hr.), then washed with water and evaporated. The crystalline residue was redissolved in dry ether, and hydrogen chloride bubbled in to precipitate the crude *dihydrochloride*. Recrystallisation of this from hydrochloric acid–acetone gave yellow aggregates (3 g.), m. p. above 180° (decomp.), fusing ~250° (Found: C, 62·2; H, 6·0; N, 9·3. $C_{16}H_{18}N_2Cl_2$ requires C, 62·2; H, 5·9; N, 9·1%).

Similarly, 5-bromomethylacridine (5·7 g.) with diethylamine (15 c.c.) in boiling benzene (150 c.c.) (2 hr.) gave *5-diethylaminomethylacridine dihydrochloride*, needles (from ethanol–ether), m. p. >180° (decomp.), fuses ~245° (Found: C, 63·7; H, 6·7; N, 8·0. $C_{18}H_{22}N_2Cl_2$ requires C, 64·1; H, 6·6; N, 8·3%).

5-Acridinylmethyltrimethylammonium Bromide.—5-Bromomethylacridine (4 g.) in boiling

[1] Part I, Campbell, Franklin, Morgan, and Tivey, *J.*, 1958, 1145; Morgan and Tivey, B.P. 789,696.
[2] Monti and Procopio, *Gazzetta*, 1933, **63**, 724.
[3] Koenigs, *Ber.*, 1899, **32**, 3599.

benzene (150 c.c.), when treated with dry trimethylamine (3 hr.), gave yellow needles of 5-*acridinylmethyltrimethylammonium bromide* (3·4 g.), m. p. ~200° (decomp.), fuses 240—245° (Found: C, 61·4; H, 5·9; N, 8·6. $C_{17}H_{19}N_2Br$ requires C, 61·6; H, 5·8; N, 8·5%).

Similarly, 5-bromomethylacridine (2·5 g.) in benzene (50 c.c.), refluxed for 2 hr. with triethylamine (10 c.c.), deposited pale yellow leaflets of *5-acridinylmethyltriethylammonium bromide* (2 g.), m. p. ~190° (decomp.), fuses ~235° (Found: C, 62·7; H, 7·0; N, 7·6. $C_{20}H_{25}N_2Br,0·5H_2O$ requires C, 62·8; H, 6·9; N, 7·3%).

5-*Acridinylmethyltrimethylammonium Methyl Sulphate*.—5-Dimethylaminomethylacridine (10 g.) in benzene (100 c.c.) was treated with dimethyl sulphate (15 c.c.) in benzene (30 c.c.) at room temperature. The crystalline precipitate which separated was recrystallised from ethanol–ether to give *5-acridinylmethyltrimethylammonium methyl sulphate* (10·7 g.), m. p. 184—186° (decomp.) (Found: C, 58·7; H, 6·4. $C_{18}H_{22}O_4N_2S,0·5H_2O$ requires C, 58·2; H, 6·0%). The latter (1 g.) was heated with dimethyl sulphate (6 c.c.) at 90° for 5 min. After cooling, the separated lower layer recrystallised from absolute ethanol–acetone, to give the *dimethosulphate*, m. p. 206—208° (decomp.) (Found: C, 47·5; H, 5·4. $C_{20}H_{28}O_8N_2S_2,H_2O$ requires C, 47·4; H, 5·6%).

3-*Chloro*-5-(2-*dimethylaminoethyl*)*acridine Dihydrochloride*.—3-Chloro-5-methylacridine (6·8 g.), hydrochloric acid (2·5 c.c.), water (40 c.c.), dimethylamine hydrochloride (3·5 g.) and 40% aqueous formaldehyde (3·5 c.c.) were refluxed together for 2 hr., cooled, and filtered and the filtrate was basified with aqueous ammonia and extracted with benzene. The benzene residue was dissolved in hydrochloric acid, and acetone added. The resultant precipitate of *3-chloro-5-(2-dimethylaminoethyl)acridine dihydrochloride* (3 g.) recrystallised from hydrochloric acid–acetone as needles, m. p. 205° (decomp.) (Found: C, 54·9; H, 5·7; N, 7·9. $C_{17}H_{19}N_3Cl_3,H_2O$ requires C, 54·5; H, 5·7; N, 7·5%).

Similarly prepared, *2-chloro-5-(2-dimethylaminoethyl)-7-methoxyacridine dihydrochloride*, m. p. ~215° (decomp.), recrystallised in yellow-orange needles from hydrochloric acid–acetone (Found: C, 53·7; H, 5·5; N, 6·8; Cl, 26·3. $C_{18}H_{21}ON_2Cl_3,H_2O$ requires C, 53·3; H, 5·7; N, 6·9; Cl, 26·2%).

2-5′-*Acridinylethyltrimethylammonium Methyl Sulphate*.—5-2′-Dimethylaminoethylacridine (5 g.) in dry benzene (80 c.c.) when shaken with dimethyl sulphate (7 c.c.), reacted exothermically and a pale yellow solid was precipitated which, when recrystallised from ethanol, gave pale yellow prisms of *2-5′-acridinylethyltrimethylammonium methyl sulphate* (7 g.), m. p. >190° (decomp.), fuses ~220° (Found: C, 60·6; H, 6·5; N, 7·4; S, 8·4. $C_{19}H_{24}O_4N_2S$ requires C, 60·6; H, 6·4; N, 7·4; S, 8·5%). Similarly, the *monomethiodide*, m. p. >220° (decomp.), fuses 228°, crystallised in pale yellow prismatic needles from ethanol (Found: C, 54·8; H, 5·4; N, 8·1; I, 31·4. $C_{18}H_{21}N_2I$ requires C, 55·1; H, 5·4; N, 7·1; I, 32·3%). The *dimethosulphate* was prepared by heating the monomethosulphate (2·6 g.) in dimethyl sulphate (15 c.c.) for a few minutes at 90°. The solidified reaction mixture crystallised from methanol in yellow needles, m. p. 161° (Found: C, 48·6; H, 5·8; N, 5·7; S, 12·5. $C_{21}H_{30}O_8N_2S_2,H_2O$ requires C, 48·5; H, 6·2; N, 5·4; S, 12·3%).

5-*Vinylacridine*.—2-5′-Acridinylethyltrimethylammonium methiodide (2·3 g.) in water (100 c.c.) was heated with 5N-sodium hydroxide (5 c.c.) on a water-bath for 0·5 hr. The mixture, when cold, was filtered to give a pale green solid (1·3 g.), m. p. 74—84°, which was dissolved in light petroleum containing 5% of benzene and purified chromatographically on alumina. Recrystallisation from light petroleum (b. p. 60—80°) then gave lemon needles of *5-vinylacridine*, m. p. 86°, resetting, and remelting at 89° [Found: C, 87·7; H, 5·5; N, 6·9%; *M* (Rast), 198. $C_{15}H_{11}N$ requires C, 87·8; H, 5·4; N, 6·8%; *M*, 205]. The *hydrochloride* crystallised from ethanol–ether in yellow needles, m. p. 232° (decomp.) (Found: Cl, 14·7. $C_{15}H_{11}N,HCl$ requires Cl, 14·7%).

5-*Ethylacridine*.—5-Vinylacridine (208 mg.) in ethanol (15 c.c.) was hydrogenated at room temperature and pressure over platinum oxide (0·1 g.). After filtration and evaporation to dryness, the ethanolic residue (200 mg.; m. p. 106—110°) was oxidised with aqueous ferric chloride in the usual manner to give, on recrystallisation from light petroleum (b. p. 60—80°), yellow needles of 5-ethylacridine (100 mg.), m. p. and mixed m. p. 110—111°. The *picrate* recrystallised from ethanol in needles, m. p. 203° (Found: N, 12·7. $C_{15}H_{13}N,C_6H_3O_7N_3$ requires N, 12·8%).

3-5′-*Acridinylpropan*-1-*ol*.—Methyl β-5′-acridinylpropionate [1] (30 g.) in dry ether (750 c.c.) was added to a suspension of lithium aluminium hydride (6·5 g.) in ether (400 c.c.), and the

mixture refluxed for 5 hr. After decomposition of the excess of hydride by Micovic and Mihailovic's method [4] the ether layer was evaporated to dryness. Recrystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave colourless needles of *3-5′-acridanylpropan-1-ol*, m. p. 116—117° (Found: C, 79·9; H, 7·2; N, 5·9. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·2; N, 5·9%). The latter (24·5 g.) was treated in boiling dilute hydrochloric acid (1200 c.c.) with powdered ferric chloride until the reaction was complete. On cooling, the mixture was basified with aqueous ammonia and the precipitate, when dried, extracted with ethyl acetate. The residue crystallised from ethyl acetate, to give yellow needles of *3-5′-acridinylpropan-1-ol*, m. p. 159—161° (Found: C, 81·1; H, 6·4; N, 5·8. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·4; N, 5·9%).

3-5′-Acridinylpropyl Bromide.—3-5′-Acridinylpropan-1-ol (24 g.), when refluxed in 48% aqueous hydrobromic acid (200 c.c.), gave, on cooling, the *bromide hydrobromide* (31·7 g.), which recrystallised in yellow needles, m. p. 238—240°, from ethanol (Found: C, 50·6; H, 4·0; N, 3·7. $C_{16}H_{15}NBr_2$ requires C, 50·4; H, 3·9; N, 4·0%). Treatment of the salt in aqueous solution with ammonia furnished *3-5′-acridinylpropyl bromide* which recrystallised in yellow needles, m. p. 103—104°, from ethanol (Found: C, 63·3; H, 4·8; N, 4·9. $C_{16}H_{14}NBr,0{\cdot}25H_2O$ requires C, 63·1; H, 4·8; N, 4·6%).

5-(3-Dimethylaminopropyl)acridine Dihydrochloride.—Dry dimethylamine was passed for 2 hr. through a stirred solution of 3-5′-acridinylpropyl bromide (30·7 g.) in ethanol (350 c.c.) at 70°. The ethanol was removed and the residue treated with 2N-sodium hydroxide and extracted with ethyl acetate. Evaporation of the ethyl acetate layer left an oil which was taken up in the minimum of hydrochloric acid and treated with acetone. The crude precipitate, when further treated with hydrochloric acid–acetone, gave yellow needles of *5-(3-dimethylaminopropyl)acridine dihydrochloride* (34 g.), m. p. 276—278° (Found: C, 58·1; H, 7·1; N, 7·3. $C_{18}H_{22}N_2Cl_2,2H_2O$ requires C, 57·9; H, 7·0; N, 7·5%).

3-5′-Acridinylpropyltrimethylammonium Methyl Sulphate.—Crude 5-(3-dimethylaminopropyl)-acridine (prepared from the foregoing hydrochloride) (21 g.) in benzene (60 c.c.) was treated with dimethyl sulphate (15 c.c.) at room temperature. The separated oil, when solid (30·7 g.), was filtered off and recrystallised from acetone–propan-2-ol, to give *3-5′-acridinylpropyltrimethylammonium methyl sulphate*, m. p. 190—192° (decomp.) (Found: C, 58·0; H, 6·7. $C_{20}H_{26}O_4N_2S,H_2O$ requires C, 58·2; H, 6·9%).

This sulphate (10 g.) was treated for 15 min. with dimethyl sulphate (4 c.c.) in boiling nitromethane (50 c.c.). On cooling, benzene was added to the mixture to give a crude product which, when recrystallised from absolute ethanol, gave pale yellow needles of the *dimethosulphate* (6·5 g.), m. p. 230—232° (decomp.) (Found: C, 46·2; H, 6·6; N, 5·0. $C_{22}H_{32}O_8N_2S_2,3H_2O$ requires C, 46·3; H, 6·7; N, 4·9%).

3-Chloro-5-(3-hydroxypropyl)acridine.—Ethyl β-(3-chloro-5-acridinyl)propionate [1] (8 g.) in tetrahydrofuran (50 c.c.) was refluxed with lithium borohydride (0·06 mol.) in tetrahydrofuran [5] (60 c.c.) for 6 hr., then decomposed,[4] and extracted with ethyl acetate. Evaporation of the extract left an oil which was oxidised by ferric chloride in the usual manner. On cooling, the yellow crystalline hydrochloride (7·4 g.), m. p. 220° (decomp.), which separated was filtered off and washed with acetone. Basification, extraction with chloroform, and recrystallisation gave pale yellow needles of the *alcohol*, m. p 189—190° (Found: C, 70·0; H, 5·3. $C_{16}H_{14}ONCl$ requires C, 70·7; H, 5·2%).

3-Chloro-5-(3-dimethylaminopropyl)acridine dihydrochloride, m. p. 270°, needles from aqueous acetone (Found: C, 58·1; H, 5·8; N, 7·5. $C_{18}H_{21}N_2Cl_3$ requires C, 58·1; H, 5·7; N, 7·5%), was prepared, as the unsubstituted analogue, by conversion of the foregoing propanol into *3-(3-chloro-5-acridinyl)propyl bromide*, m. p. 83—85°, needles from light petroleum (b. p. 60—80°) (Found: C, 57·3; H, 4·0. $C_{16}H_{13}NBrCl$ requires C, 57·4; H, 3·9%), and treatment of this with dimethylamine in ethanol at 70°.

Methyl γ-5-Acridinylbutyrate.—5-2′-Hydroxyethylacridine (114 g.) in chloroform (950 c.c.) was refluxed with thionyl chloride (175 c.c.) for 2 hr. On cooling, the crystalline hydrochloride was filtered off and dried (yield, 168 g.), powdered, and added to a stirred solution of sodium (59·4 g.) and diethyl malonate (420 c.c.) in ethanol (800 c.c.), and the mixture was refluxed for 5 hr. On cooling, hydrochloric acid–water (1 : 1; 1 l.) was added, the ethanol was distilled off, and the aqueous residue refluxed for 2 hr. This solution deposited a crystalline hydrochloride

[4] Micovic and Mihailovic, *J. Org. Chem.*, 1953, **18**, 1192.
[5] Paul and Joseph, *Bull. Soc. chim.*, 1953, 758.

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(125 g.), m. p. 267—270°, on cooling, a solution of which (65 g.) in aqueous sodium hydroxide (250 c.c.) was diluted with water (250 c.c.) and acidified with glacial acetic acid (290 g.). The resultant precipitate, when dried and recrystallised from acetic acid, gave γ-5′-acridinylbutyric acid, m. p. >220° (decomp.). Esterification in the usual manner furnished the *methyl ester*, m. p. 92—93°, in rectangular plates [from light petroleum (b. p. 60—80°)] (Found: C, 77·8; H, 6·3; N, 5·1. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

5-(4-Dimethylaminobutyl)acridine Dihydrochloride.—Reduction of this ester with lithium aluminium hydride gave *4-5′-acridinylbutan-1-ol*, m. p. 117—119°, leaflets from benzene (Found: C, 80·4; H, 7·7; N, 5·5. $C_{17}H_{19}ON$ requires C, 80·6; H, 7·6; N, 5·5%), and this on oxidation furnished *4-5′-acridinylbutan-1-ol*, m. p. 146—147°, yellow needles from ethyl acetate (Found: C, 81·2; H, 6·7; N, 5·7. $C_{17}H_{17}ON$ requires C, 81·2; H, 6·8; N, 5·6%). The last compound was converted into *4-5′-acridinylbutyl bromide hydrobromide*, m. p. 213—215° (decomp.), yellow needles from ethanol (Found: C, 51·8; H, 4·3; N, 3·5. $C_{17}H_{17}NBr_2$ requires C, 51·9; H, 4·4; N, 3·6%), and this with dimethylamine, as above, gave *5-(4-dimethylaminobutyl)acridine dihydrochloride*, m. p. 226—228°, yellow needles from ethanol–ether (Found: C, 64·7; H, 7·0; N, 7·9. $C_{19}H_{24}N_2Cl_2$ requires C, 65·0; H, 6·9; N, 8·0%).

4-5′-Acridinylbutyltrimethylammonium methyl sulphate, m. p. 198—200°, pale yellow needles (from ethanol) (Found: C, 62·4; H, 6·9; N, 6·8. $C_{21}H_{28}O_4N_2S$ requires C, 62·4; H, 7·0; N, 6·9%), and the corresponding *dimethosulphate*, m. p. 152—155°, yellow prisms (from ethanol) (Found: C, 51·5; H, 6·9; N, 4·8. $C_{22}H_{34}O_8N_2S_2,0{\cdot}5H_2O$ requires C, 51·2; H, 6·5; N, 5·2%), were obtained as above.

The authors thank Dr. R. E. Bowman for advice.

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283. *Methyl Ethers of* L-*Fucose.*

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The four methyl L-fucosides have been synthesised and separated on cellulose. Partial methylation of methyl β-L-fucofuranoside and of methyl α-L-fucopyranoside followed by hydrolysis and separation on cellulose have led to the isolation of eight of the eleven possible methyl ethers of fucose.

THE occurrence of L-fucose in a variety of natural polysaccharides led to this study of the properties of its methyl ethers. Treatment with 0·8% methanolic hydrogen chloride at room temperature until the rotation reached a maximum positive value gave the best yield (64·6%) of methyl α- and β-L-furanosides. The product after separation on a cellulose column gave methyl β-L-fucofuranoside (44%), α-L-fucofuranoside (20·6%), α-L-fucopyranoside (15·4%), and β-L-fucopyranoside (20%).

While this work was in progress Miss Watkins [1] recorded the separation of the four glycosides after treatment of fucose with hot 0·025% methanolic hydrogen chloride but she gave no indication of the relative proportions of the four products. We found that glycosidation in the hot gave a higher proportion of pyranosides.

Incomplete methylation of methyl β-L-fucofuranoside and of α-L-fucopyranoside with Purdie reagents followed by hydrolysis and partition on cellulose led to the isolation of the methylated fucoses shown in the Table.

Bell and Dedonder [2] have shown that sugars substituted at the position adjacent to the reducing group do not form a water-insoluble formazan with triphenyltetrazolium hydroxide and that a paper chromatogram sprayed with this reagent reveals only those reducing aldoses in which position 2 is unsubstituted. Only those derivatives marked with an asterisk in the Table gave red spots in this way.

[1] Watkins, *J.*, 1955, 2054.
[2] Dedonder, personal communication quoted by Bell in "Modern Methods of Plant Analysis," ed. Paech and Tracey, Springer-Verlag, Berlin, Vol. II, p. 9; Bell and Dedonder, *J.*, 1954, 2866.

The only methyl ether of L-fucose which was not obtained was the 4-*O*-methyl-L-fucose. In keeping with the recognised reactivity at position 2 in sugars it is noteworthy that the 2-*O*-mono- and 2 : 3-di-*O*-methyl ethers were obtained in highest yield from both methylations. Whereas the methyl ethers with a pyranose structure all had negative rotations, those containing a furanose ring were positive.

	Fraction numbers †	From β-L-fucofuranoside (%)	Fraction numbers †	From α-L-fucopyranoside (%)
2 : 3 : 4-Tri-*O*-methyl-L-fucose	—	—	P1	5·5
2 : 3 : 5-Tri-*O*-methyl-L-fucose	F1	5·5	—	—
2 : 3-Di-*O*-methyl-L-fucose	F3	17·5	P2(a)	27·5
2 : 4-Di-*O*-methyl-L-fucose	—	—	P3	11·5
2 : 5-Di-*O*-methyl-L-fucose ..... } 3 : 5-Di-*O*-methyl-L-fucose * ..... }	F2	19·0	—	—
3 : 4-Di-*O*-methyl-L-fucose *	—	—	P4	2·5
5-*O*-Methyl-L-fucose *	F4	7·0	—	—
2-*O*-Methyl-L-fucose	F5	36·0	P5	43·5
3-*O*-Methyl-L-fucose *	F6	15·0	P7	9·5

† See Experimental.

2 : 3 : 5-Tri-*O*-methyl-L-fucose was prepared by methylation of methyl β-L-fucofuranoside in dimethylformamide. Complete methylation proved difficult and after removal of the glycosidic methoxyl group the tri-*O*-methylfucose was separated from less methylated derivatives by partition on a cellulose column. It gave correct analyses for a tri-*O*-methyl-L-fucose and did not reduce periodate. It was an exceedingly hygroscopic and volatile syrup.

The first fraction (F1) separated as a syrup from the partition of the hydrolysate of the partly methylated furanoside, gave a single spot on ionophoresis, was chromatographically identical with the above 2 : 3 : 5-tri-*O*-methyl-L-fucose, and did not reduce periodate. Owing to its high volatility it was exceedingly difficult to dry and a large proportion was lost in an attempt to dry it over phosphoric oxide in a vacuum-desiccator. Consequently the recorded rotation and methoxyl contents are on moisture-containing material.

Fraction F3 and fraction P2(a) (Table) had $[\alpha]_D$ −97° and −100° respectively (cf. 2 : 3 : 4-tri-*O*-methylfucose, $[\alpha]_D$ −128°). They both gave correct analyses for di-*O*-methyl derivatives and had identical properties. The only dimethylfucose which can be synthesised from both a fucofuranoside and a fucopyranoside is the 2 : 3-di-*O*-methyl derivative. Further proof of the structure was obtained by oxidative preparation of D(−)-dimethoxysuccinic acid and its crystalline amide. The syrupy lactone, $[\alpha]_D$ +10° ⟶ +50° (96 hr.), isolated after oxidation of the dimethyl-sugar with bromine water was undoubtedly a furanolactone.[3] It is clear that the supposed 2 : 3-di-*O*-methyl-L-fucose ($[\alpha]$ +4·6°) isolated from methylated fucoidin by Conchie and Percival [3] by hydrolysis of fraction B contained a considerable quantity of impurity. Indeed these authors comment on the very low yield of D(−)-dimethoxysuccindiamide they isolated after oxidation of their material.

From the fucopyranoside hydrolysate crystalline 3 : 4- and 2 : 4-di-*O*-methyl-L-fucose were also separated. The former was identical with authentic material.[4] This 2 : 4-di-*O*-methyl-L-fucose was characterised by its methoxyl content and its resistance to periodate. The rotation ($[\alpha]_D$ −27° ⟶ −15°) of the derived lactone indicated a 1 : 5-ring structure. The di-*O*-methylfucose isolated from the methylated extracellular polysaccharide of *Aerobacter aerogenes* by Aspinall, Jamieson, and Wilkinson [5] and thought from the available evidence to be the 3 : 5-di-*O*-methyl-L-fucose has now been shown to be 2 : 4-di-*O*-methyl-L-fucose.

[3] Conchie and Percival, *J.*, 1950, 827.
[4] Percival and Percival, *J.*, 1950, 690.
[5] Aspinall, Jamieson, and Wilkinson, *J.*, 1956, 3483.

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Fraction F2 (Table) gave a single spot on a paper chromatogram irrigated with solvents (1), (2), or (3) (see below), gave a red spot on a paper chromatogram sprayed with triphenyltetrazolium hydroxide, and gave analyses correct for a di-*O*-methylfucose. However, on paper ionophoresis [6] (borate buffer, pH 10) two spots were obtained with M_G 0·65 and 0·02. Foster [7] attributes high mobility under these conditions of ionophoresis to the presence of free hydroxyl groups on $C_{(1)}$ and $C_{(2)}$ and the ability of the substance to form complexes across these two atoms. He has shown that neither 2 : 3- nor 2 : 4-di-*O*-methylrhamnose ($M_G < 0·05$) has an appreciable mobility and that of the 2 : 3-, 2 : 4-, and 3 : 4-di-*O*-methylglucoses only the latter has an M_G (0·31) at all comparable with that recorded by us for this fraction. It appears therefore that the spot of M_G 0·65 corresponds to the 3 : 5-di-*O*-methyl-L-fucose and that the spot of M_G 0·02 is due to the presence of some 2 : 5-di-*O*-methyl-L-fucose.

Crystalline 2-*O*-methyl- [8] and 3-*O*-methyl-L-fucose [3] (the latter crystalline for the first time) were isolated from the hydrolysates of both methylated fucosides. In addition 5-*O*-methyl-L-fucose has been separated and characterised.

The reduction of periodate by each of the methylated derivatives was measured.[9] 2 : 3 : 5-Tri-*O*-methyl- and 2 : 4-di-*O*-methyl-fucose, in keeping with their structures, were not oxidised; of the remaining derivatives only the mixture of 2 : 5- and 3 : 5-dimethyl ethers and the 3 : 4-di-*O*-methylfucose were reduced in an approximately theoretical manner. Anomalous results have previously been obtained for partly methylated 6-deoxyhexoses [3,4] and hexoses.[10]

Experimental

Evaporations were done at 40° under reduced pressure. Paper-partition chromatography was done on Whatman No. 1 filter paper with the upper layers of the following v/v solvent systems: (1) butan-1-ol–ethanol–water (4 : 1 : 5), (2) benzene–butan-1-ol–pyridine–water (1 : 5 : 3 : 3), (3) ethyl methyl ketone half saturated with water plus ammonia (99 : 1); and the reducing sugars were located by aniline oxalate (AO), and the non-reducing sugars with aniline oxalate containing 3% (v/v) syrupy phosphoric acid (AP). Methylated sugars in which position 2 was unsubstituted were revealed by triphenyltetrazolium hydroxide.[11] R_G, R_F, and R_{fu} are the rates of travel relative to tetramethylglucose, the solvent front, and fucose respectively. Ionophoresis was carried out according to the conditions used by Percival and Fisher.[6] Rotations were measured in water at 18°.

Preparation of Methyl L-*Fucosides.*—(A) L-Fucose (m. p. 145°) (10 g.) was dissolved in 0·8% methanolic hydrogen chloride (400 c.c.) at 15° and the change in rotation followed polarimetrically to a maximum $[\alpha]_D$ of +10·4° (66 hr.). Neutralisation with silver carbonate and evaporation of the filtrate gave a syrup (10·80 g.).

(B) L-Fucose (2 g.) in dry methanol (80 c.c.) was agitated with Amberlite resin (IR-100H) (3 g.) at 15°. After 13 days the solution had a maximum rotation of $[\alpha]_D$ +8·0°. Removal of solvent gave a syrup (2·19 g.). Paper chromatography of both syrups with solvent (1) for 40 hr. and spray (AP) showed 4 components with R_F 0·57, 0·51, 0·44, and 0·39 respectively. In addition, the syrup B, $[\alpha]_D$ +8·0°, contained a little free fucose.

The syrup A (2 g.) was separated on a cellulose column (85 × 2·7 cm.) by using ethyl methyl ketone saturated with water. Four fractions were collected and their R_G values measured with solvent (1). Fractions II, III, and IV were recrystallised from methanol: fraction I (0·7—1·1 l.), syrupy methyl β-L-fucofuranoside (0·86 g.), R_G 0·70, $[\alpha]_D$ +112° (*c* 7·0); fraction II (1·6—1·92 l.), methyl α-L-fucofuranoside (0·40 g.), R_G 0·62, m. p. 127—128°, $[\alpha]_D$ −108° (*c* 2·0), −115° (*c* 2·0 in MeOH); fraction III (2·14—2·44 l.), methyl α-L-fucopyranoside (0·30 g.), R_G 0·53, m. p. 158—159°, $[\alpha]_D$ −191° (*c* 2·0); fraction IV (2·551—4·0 l.), methyl β-L-fucopyranoside (0·38 g.), R_G 0·48, m. p. 126—127°, $[\alpha]_D$ +10·5 (*c* 1·0). After addition of ethyl methyl ketone (50 c.c.)

[6] Fisher and Percival, *J.*, 1957, 2666.
[7] Foster, *J.*, 1953, 982; Foster and Stacey, *J.*, 1955, 1778.
[8] Nelson and Percival, *J.*, 1957, 2191.
[9] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.
[10] Jeanloz, *Helv. Chim. Acta*, 1944, **27**, 1509; Bell, *J.*, 1948, 992; Greville and Northcote, *J.*, 1952, 1945.
[11] Wallenfels, *Naturwiss.*, 1950, **37**, 491.

the initial syrup A, $[\alpha]_D$ +10·5° (5 g.), deposited crystals of methyl α-L-fucopyranoside (0·47 g.), m. p. and mixed m. p. 158—159°.

Partial Methylation of Methyl β-L-*Fucofuranoside.*—The furanoside (3 g.) was methylated twice with methyl iodide (60 c.c.) and silver oxide (11·5 g.) at 45°. The product was heated at 100° with 0·3N-sulphuric acid (150 c.c.) until the rotation was constant (45 min.). Neutralisation, with barium carbonate, of the cooled solution, filtration, and evaporation gave a syrup (2·6 g.). Chromatographic analysis [solvent (1)] showed 7 spots. This syrup (2·5 g.) was separated on a cellulose column (85 × 3 cm.) with light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3, v/v) saturated with water. After 3 l. had been collected the ratio of solvents was changed to 6·5 : 3·5, after another 2·5 l. to 6 : 4, and after another 1·5 l. finally to 1 : 1. The following fractions were collected. Each fraction appeared to be homogeneous and gave a single spot on paper chromatograms run in solvents (1), (2), and (3). The R_G values given are for solvent (1).

Fraction F1 (0·60—1·28 l.), a hygroscopic syrup (0·109 g.), R_G 1·05, $[\alpha]_D$ +47° (*c* 1·0), M_G 0·0 {2 : 3 : 5-tri-*O*-methyl-L-fucose had R_G 1·05, $[\alpha]_D$ +70° (*c* 1·3)} (Found: OMe, 36·3. Calc. for $C_9H_{18}O_5$: OMe, 45·1%); this syrup showed no appreciable reduction of periodate on prolonged standing with the oxidant.

Fraction F2 (1·30—2·00 l.), a syrup (0·384 g.), had R_G 0·92, M_G (two components) 0·65, 0·02, $[\alpha]_D$ +38° (*c* 2·5) (Found: OMe, 32·3. Calc. for $C_8H_{16}O_5$: OMe, 32·0%). One mole of this dimethyl sugar reduced the following number of moles of periodate: 0·36 (18 hr.); 0·46 (42 hr.); 0·71 (90 hr.); 1·04 (180 hr.). A portion of the syrup (90 mg.) was oxidised with bromine water at 37°. After 5 days the solution no longer reduced Fehling's solution. Treatment in the usual manner gave a mixture of syrupy lactones, $[\alpha]_D$ +20° ⟶ +36°.

Fraction F3 (2·50—3·50 l.), syrupy 2 : 3-*di*-O-*methyl*-L-*fucose* (0·3516 g.), had R_G 0·75, $[\alpha]_D$ −97° (*c* 3·0) (Found: OMe, 31·5. $C_8H_{16}O_5$ requires OMe, 32·05%). One mole reduced 0·23 (18 hr.), 0·39 (42 hr.), 0·64 (90 hr.), 0·82 (180 hr.) mole of periodate. Oxidation of a portion (0·05 g.) with bromine water at 37° for 6 days gave a syrupy lactone which had $[\alpha]_D$ +10° ⟶ +50° (96 hr.) (*c* 2·0). A portion (0·409 g.) was converted into D(−)-αβ-dimethoxysuccindiamide by oxidation first with 0·6M-sodium metaperiodate (25 c.c.) and then with bromine (7 days) according to the conditions used by Arni and Percival [12] for the oxidation of 3 : 4-di-*O*-methylfructose. Distillation of the ester (0·23 g.) (bath temp. 150°/0·05 mm.) gave a mobile syrup (0·158 g.), n_D^{20} 1·4318, $[\alpha]_D$ −73° (*c* 1·0 in MeOH). The derived amide (67 mg. from 97 mg.) had $[\alpha]_D$ −90° (*c* 0·6), m. p. and mixed m. p. with D(−)-dimethoxysuccindiamide 278°. Mixed m. p. with (±)-dimethoxysuccindiamide 240—246°.

Fraction F4 (3·92—4·56 l.), syrupy 5-O-*methyl*-L-*fucose* (0·1404 g.), had R_G 0·70, $[\alpha]_D$ +28·3° (*c* 0·8) (Found: OMe, 17·2. $C_7H_{14}O_5$ requires OMe, 17·4%). One mole reduced 1·83 (0·5 hr.), 1·99 (1·75 hr.), 2·22 (5·75 hr.), 2·70 (25 hr.), 2·70 (48 hr.) moles of periodate. The derived osazone had m. p. 190° and gave a positive test for OMe.

Fraction F5 (6·00—8·56 l.), 2-*O*-methylfucose (0·7262 g.), had R_G 0·60, m. p. and mixed m. p. 151°, $[\alpha]_D$ −87·2° (*c* 1·4). One mole reduced 1·04 (0·5 hr.), 1·17 (1·3 hr.), 1·30 (3·08 hr.), 1·98 (7 hr.), 2·93 (18 hr.), 3·8 (470 hr.) moles of periodate.

Fraction F6 (10·92—11·72 l.), syrupy 3-*O*-methyl-L-fucose (0·3056 g.), had R_G 0·48. This fraction crystallised when seeded with a crystal of Fraction P7 and had m. p. and mixed m. p. 110°, $[\alpha]_D$ −97° (*c* 1·0). One mole used 0·91 (18 hr.), 0·96 (42 hr.), 1·21 (90 hr.), 1·27 (160 hr.) moles of periodate. For further characterisation see Fraction P7.

Fucose (0·17 g.) was recovered from the water-washings of the column.

Partial Methylation of Methyl α-L-*Fucopyranoside.*—The pyranoside (5 g.) was methylated thrice with methyl iodide (40 c.c.) and silver oxide (10 g.) at 45°. Hydrolysis of the product as for the methylated furanoside gave a syrup (4·6 g.) which showed 7 spots on chromatography. The syrup was separated on a cellulose column with light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3, v/v) saturated with water. After 2·25 l. had been collected the ratio of solvents was changed to 6·5 : 3·5 and after another 1 l. had passed to 6 : 4 (5·75 l.). The R_G and R_F values of each fraction were measured in solvents (1) and (2) respectively.

Fraction P1 (1·00—1·40 l.), syrupy 2 : 3 : 4-tri-*O*-methyl-L-fucose (0·123 g.), had R_G 0·92, R_F 0·79, $[\alpha]_D$ −128° (*c* 1·1). Chromatography showed a single spot in solvents (1), (2), and (3), identical with those of authentic 2 : 3 : 4-tri-*O*-methyl-L-fucose. The derived glycoside after purification by sublimation had m. p. and mixed m. p. 95—96°, $[\alpha]_D$ −200° (*c* 1·0).

[12] Arni and Percival, *J.*, 1951, 1822.

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Fraction P2 (1·70—2·22 l.) was a syrup (0·928 g.), R_G 0·75, R_F 0·70, $[\alpha]_D$ −106° (*c* 7·7). Paper chromatography [solvent (3)] showed two spots, of R_F 0·47 and 0·32. This fraction (0·70 g.) was partitioned on a cellulose column (40 × 1·5 cm.) with solvent (3) and collected in 20 c.c. fractions. The solvent was removed from the respective fractions at 40° in a stream of nitrogen. Fraction P2(a) (180—240 c.c.) was syrupy 2 : 3-di-*O*-methyl-L-fucose (0·348 g.), $[\alpha]_D$ −95° ⟶ −100° (19 hr. const.) (*c*, 2·1). Chromatographic analysis showed a single spot in solvents (1), (2), and (3) identical with the spot given by fraction F3. The R_F in solvent (3) was 0·47 (Found: OMe, 30·5. Calc. for $C_8H_{16}O_5$: OMe, 32·2%). The syrup consumed 0·44 (43 hr.), 0·66 (55 hr.), 0·8 (160 hr.) mole of periodate per $C_8H_{16}O_5$ unit. Fraction P2(b) (260—280 c.c.) was a syrup (0·144 g.), shown by paper chromatography [solvent (3)] to be a mixture of fractions P2(a) and P2(c). Fraction P2(c) (300—400 c.c.) was a syrup (0·73 g.) which crystallised and had m. p. and mixed m. p. 131—132° with fraction P3 [recrystallised from chloroform–light petroleum (b. p. 40—60°)].

Fraction P3 (2·25—2·75 l.) was 2 : 4-*di*-O-*methyl*-L-*fucose* (0·127 g.), R_G 0·75, R_F 0·73, m. p. 131—132° [recrystallised from chloroform–light petroleum (b. p. 40—60°)], $[\alpha]_D$ −85° (*c* 0 85) (Found: OMe, 32·0%). This dimethyl-sugar was not oxidised by periodate during 300 hr.

Fraction P4 (3·15—4·00 l.) was 3 : 4-di-*O*-methyl-L-fucose (0 051 g.), R_G 0·7, R_F 0·67, m. p. and mixed m. p. 82° (cf. ref. 4). It moved at the same speed on a paper chromatogram as authentic 3 : 4-di-*O*-methyl-L-fucose in solvents (1), (2), and (3) and had $[\alpha]_D$ −118° (*c* 2·2). One mole took up 0·85 mole of periodate (55 hr.), 0·95 mole (160 hr.).

Fraction P5 (4·50—6·70 l.) was 2-*O*-methyl-L-fucose (0·932 g.), R_G 0·56, R_F 0·63, m. p. and mixed m. p. 150—152° (recrystallised from ethanol), $[\alpha]_D$ −68° (20 min.) ⟶ −85° (2·5 hr. const.) (*c* 1·0), −42° (*c* 1·0 in EtOH). The derived fucoside (2% MeOH–HCl under reflux) had $[\alpha]_D^{18}$ −57·7° (*c* 0·52) and reduced 0·45 (9 hr.), 0·67 (48 hr.) mole of periodate for every $C_8H_{16}O_5$ unit.

Fraction P6 (6·70—82·0 l.) was a colourless syrup (0·244 g.) shown by paper chromatography to be a mixture of fractions P5 and P7.

Fraction P7 (8·20—9·05 l.) was syrupy 3-*O*-methyl-L-fucose (0·59 g.), R_G 0·45, R_F 0·56, which crystallised slowly, then having m. p. 109—110°, $[\alpha]_D$ −97° (*c* 4·2), −60·8° (*c* 3·8 in EtOH) (Found: OMe, 17·8. Calc. for $C_7H_{14}O_5$: OMe, 17·4%). The derived osazone had m. p. 175°. The derived syrupy glycoside (2% MeOH–HCl under reflux) had $[\alpha]_D$ −66° (*c* 1·1) and did not reduce periodate.

Fraction P8 (9·05—10·50 l.) was fucose (0·6588 g.), m. p. and mixed m. p. 143°.

2 : 3 : 5-*Tri*-O-*methyl*-L-*fucose*.—Methyl β-L-fucofuranoside (0·60 g.), stirred vigorously with redistilled dimethylformamide (20 c.c.) and methyl iodide (5 c.c.), was treated with silver oxide (5 g.) added in small portions during 30 min.[13] The stirring was continued at room temperature for 17 hr. Inorganic salts were removed and washed with dimethylformamide (2 × 7 c.c.) and chloroform (4 × 15 c.c.), and residual silver salts were removed from the solution and washings by agitation with 1% aqueous sodium cyanide (50 c.c.). The organic phase was separated and the aqueous phase extracted with chloroform (6 × 20 c.c.). The combined solution and extracts were concentrated to a syrup and the methylation was repeated (yield, 0·66 g. Found: OMe, 48·2%). Hydrolysis with 0·3N-sulphuric acid (50 c.c.) at 100° for 30 min. gave a reducing syrup (0·50 g.). Paper chromatography with solvent (1) showed three components with R_{fu} 2·31, 2·70, and 3·03 respectively. Separation of a portion (0·40 g.) on a cellulose column (38 × 2·2 cm.) with butan-1-ol–light-petroleum (b. p. 100—120°) (70 : 30 v/v) gave a fraction, syrupy 2 : 3 : 5-*tri*-O-*methyl*-L-*fucose* (0·27 g.) which gave a single pinkish-red spot on chromatography, R_{fu} 3·03 [solvent (1); spray AO], had n_D^{25} 1·4452, $[\alpha]_D^{18}$ +70° (*c* 1·5), +55° (*c* 1·4 in EtOH) (Found: OMe, 44·8. $C_9H_{18}O_5$ requires OMe, 45·1%), and did not reduce periodate.

The authors are grateful to Professor E. L. Hirst, F.R.S., for his interest and advice, the Institute of Seaweed Research for the gift of L-fucose, and the Rockefeller Foundation for a grant.

Department of Chemistry, University of Edinburgh. [*Received, November 25th*, 1957.]

[13] Kuhn, *Chem. Ber.*, 1955, **88**, 1540.

284. Solanum *Alkaloids. Part XII.* Solasodamine, a New Tetrasaccharide Derivative of Solasodine, from* S. auriculatum, S. sodomaeum, *and* S. marginatum.

By Lindsay H. Briggs and E. G. Brooker.

A new tetrasaccharide derivative of solasodine, named solasodamine, has been isolated from the green fruit of *S. auriculatum*, *S. sodomaeum*, and *S. marginatum* by an improved extraction procedure. The carbohydrate component is formed from glucose (1 mol.), galactose (1 mol.), and rhamnose (2 mols.).

In a further attempt to obtain the glycosidic alkaloid solauricine [1] from *S. auriculatum*, a product contaminated with partially hydrolysed glycosides was obtained. The berries extracted had been minced, dried, and stored for several years and it appeared that enzymic hydrolysis occurred during storage. Hence another extraction procedure was developed to obviate enzymic hydrolysis.

Fresh green berries were cut in halves and immediately placed in boiling methanol, and after extraction the glycosidic alkaloid was precipitated in the presence of methanol. Thus a new glycosidic alkaloid, m. p. 298—300°, named solasodamine, was isolated. Hydrolysis with 5% hydrochloric acid in ethanol gave solasodine and a mixture of sugars, shown to be glucose, galactose, and rhamnose by paper chromatography. Analyses of the glycoside and its picrate and picrolonate agree for the formula, $C_{51}H_{83}O_{20}N$, in accordance with the combination of solasodine with glucose, galactose, and two mols. of rhamnose. Quantitative separation of rhamnose, on a cellulose column, from the sugars obtained on hydrolysis, confirmed the presence of 2 mols. of rhamnose. Further work to elucidate the structure of the glycosidic moiety is in progress.

By the new technique, solasodamine has also been obtained from the fresh green fruits of *S. sodomaeum* and *S. marginatum*. The melting points of the glycosides and those of their picrates and picrolonates were similar. There were no differences in infrared spectra, *X*-ray powder photographs, pK_b values, and specific optical rotations of the three glycosides and they behaved identically on hydrolysis and on periodate oxidation (production of 2 mols. of formic acid and consumption of 6 mols.).

However, the new technique afforded only solasonine from fresh green berries of *S. aviculare*, and only solanine from those of *S. tuberosum*.

The isolation of solasodamine from *S. sodomaeum* suggested that in the earlier isolation of solasonine [2] hydrolysis had occurred with removal of a rhamnose group. That this assumption is not necessarily correct, however, was shown by the isolation of both solasodamine and solamargine from *S. marginatum* by the new procedure. Solasodamine was obtained from green fruit collected in August and solamargine from green fruit collected in April. Enzymic hydrolysis of rhamnose from solasodamine could not yield solamargine. Hydrolysis of pure solamargine affords only glucose and rhamnose as well as solasodine. However, when unpurified samples of solamargine (obtained by the earlier procedure [3]) were hydrolysed, traces of galactose appeared in chromatograms of the sugar mixtures, along with glucose and rhamnose. It appears, therefore, that trisaccharide and tetrasaccharide derivatives of solasodine may co-exist in the plant and that the combination of sugars is not static.

* Part XI, *J.*, 1953, 2833.

[1] Bell, Briggs, and Carroll, *J.*, 1942, 12.
[2] Briggs, Newbold, and Stace, *J.*, 1942, 3.
[3] Briggs, Brooker, Harvey, and Odell, *J.*, 1952, 3587.

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Experimental

M. p.s marked * were taken in evacuated capillaries. Rotations were determined for MeOH solutions. The infrared spectra were measured with a Beckman IR.2 spectrophotometer. Paper chromatography of sugar solutions was carried out by the descending method on Whatman No. 1 paper with butan-1-ol–pyridine–water (3 : 1 : 1) as developing solvent and aniline hydrogen phthalate solution as spray reagent. Microanalyses are by Dr. A. D. Campbell, University of Otago. Compounds were dried overnight at 100° *in vacuo* over P_2O_5 before analysis.

Isolation of Solasodamine.—(a) *From* S. auriculatum. Fresh green berries, collected at Auckland in June, were coarsely minced and immediately extracted with boiling methanol for 2 hr. The filtered extract was concentrated under reduced pressure under an anti-foaming device and completely dissolved in 3% aqueous acetic acid. Concentrated aqueous ammonia was added to the boiling solution, and the coagulated precipitate collected after cooling. The almost colourless precipitate was redissolved in 3% aqueous acetic acid and again precipitated with ammonia. Repeated crystallisation from aqueous methanol (50%) gave colourless, rectangular plates of *solasodamine*, m. p. 298—300°* (decomp.), $[\alpha]_D^{20}$ −71·6° (*c* 0·447), pK_b 6·23[4] (Found: C, 59·7; H, 8·4; N, 1·5. $C_{51}H_{83}O_{20}N$ requires C, 59·5; H, 8·1; N, 1·4%). The *picrate*, prepared in and recrystallised from aqueous ethanol (30%) in the presence of a slight excess of picric acid, formed yellow needles, m. p. 205°* (decomp.) (Found: C, 54·0; H, 7·2; N, 4·0. $C_{51}H_{83}O_{20}N,C_6H_3O_7N_3$ requires C, 54·4; H, 6·9; N, 4·4%). The *picrolonate*, prepared in and recrystallised from aqueous ethanol (80%), formed yellow, rectangular plates, m. p. 229—230°* (decomp.) (Found: C, 56·2; H, 6·9; N, 5·7. $C_{51}H_{83}O_{20}N,C_{10}H_8O_5N_4$ requires C, 56·6; H, 7·1; N, 5·4%).

(b) *From* S. sodomaeum. Fresh green berries, collected at Mt. Wellington, near Auckland, in August and extracted as in (a), gave rectangular plates, m. p. 302°* (decomp.), $[\alpha]_D^{20}$ −72·8° (*c* 0·194), pK_b 6·32 (Found: C, 59·8, 59·8; H, 8·2, 8·2; N, 1·1%). The picrate had m. p. 209° (decomp.) (Found: C, 55·0, 55·0; H, 6·95, 6·9; N, 4·6%) and the picrolonate, m. p. 237—238° (decomp.) (Found: C, 56·6, 56·9; H, 7·3, 7·2; N, 5·8%).

(c) *From* S. marginatum. Fresh green berries, collected at Mt. Wellington in August, on extraction gave rectangular plates, m. p. 301—302°* (decomp.), $[\alpha]_D^{20}$ −71·7° (*c* 0·446), pK_b 6·18 (Found: C, 60·5, 60·55; H, 8·0, 8·4; N, 1·4%). The picrate had m. p. 203° (decomp.) (Found: C, 54·4; H, 6·95; N, 4·85%) and the picrolonate, m. p. 235° (decomp.) (Found: C, 56·9; H, 7·3; N, 5·2%).

The infrared absorption spectra (Nujol mull) of solasodamine from the three species were identical: bands (in KBr) at 3472, 2941, 2890(i), 1684, 1656, 1631, 1458, 1437(i), 1377, 1342, 1309, 1292, 1245, 1190, 1170, 1139, 1088, 1056, 1019, 1003, 978, 965, 931, 896, 882, 837, 808(i), 792, and 755 cm.$^{-1}$ (i = inflexion).

X-Ray powder photographs of the glycosidic alkaloid from each species (8 hr.; copper *K*; sin θ observed up to 45°) were indistinguishable.

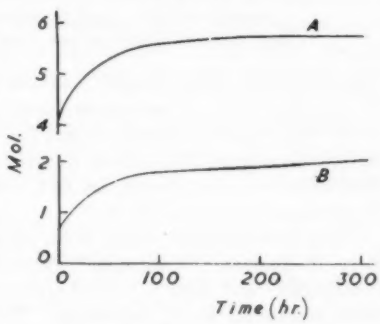
Hydrolysis of Solasodamine. Solasodamine (1 g.; from each species in separate experiments) was refluxed in concentrated hydrochloric acid (2 c.c.) and ethanol (20 c.c.) for 2 hr. at 100°. Colourless needles of solasodine hydrochloride were formed after 1½ hr. The mixture was heated with excess of ammonia solution at 100° for 1 hr.; the solid product, on repeated crystallisation from methanol and finally acetone, gave solasodine as colourless hexagonal plates, m. p. and mixed m. p. 200—201°*, infrared bands (in KBr) at 3472, 2941, 2890(i), 1684, 1656, 1631, 1458, 1437(i), 1377, 1342, 1309, 1292, 1245, 1190, 1170, 1139, 1088, 1056, 1019, 1003, 978, 965, 931, 896, 882, 837, 808(i), 792, and 755 cm.$^{-1}$. The picrate had m. p. and mixed m. p. 144—145° (decomp.).

In a simliar experiment, the hydrochloride was removed and washed with water. The combined filtrate and washings were heated for a further hour at 100°, the ethanol being allowed to evaporate, and after removal of a further crop of hydrochloride the filtrate was neutralised (Amberlite I.R.A.-400 ion-exchange resin) and concentrated *in vacuo* at room temperature to *ca.* 1 c.c. Paper chromatography of this solution showed the presence of glucose, galactose, and rhamnose.

Periodate Oxidation of Solasodamine.—Solasodamine (0·5230 g.), previously dried at 110° for 43 hr. *in vacuo* over magnesium perchlorate, was dissolved in 0·0238N-formic acid (30 c.c.; 1·4 mol.), 0·034M-sodium metaperiodate (150 c.c., 10 mol.) added, and the volume made up to

500 c.c. with water. All solutions were held overnight at 25° before mixing. The final solution was held at 25° and the periodate consumed and formic acid produced were determined in aliquot parts at intervals.[5,6] Results (see p. 1419) were identical with material from each source.

Examination of the Green Berries of S. marginatum *collected at a Different Season.*—Fresh green berries, collected at Mt. Wellington in April, were extracted by the above procedure. The product, after five recrystallisations from aqueous ammonia–ethanol (50%), yielded colourless pointed plates of solamargine, m. p. 302°* (decomp.), $[\alpha]_D^{17}$ −104° (*c* 1·561) (lit.,[3] m. p. 301°, $[\alpha]_D$ −105°) (Found: C, 62·2, 62·4; H, 8·6, 8·5; N, 1·6. Calc. for $C_{45}H_{73}O_{15}N$: C, 62·3; H, 8·5; N, 1·6%). The infrared spectrum could not be distinguished from that of solasodamine. The picrate formed rectangular yellow plates, m. p. 185°* (decomp.) (lit.,[3] m. p. 188—189°) (Found: C, 55·7; H, 6·6. Calc. for $C_{45}H_{73}O_{15}N,C_6H_3O_7N_3$: C, 55·8; H, 6·9%). The picrolonate formed yellow needles, m. p. 199—200°* (decomp.) (lit.,[3] m. p. 204—205°) (Found: C, 58·3; H, 6·9. Calc. for $C_{45}H_{73}O_{15}N,C_{10}H_8O_5N_4$: C, 58·3; H, 7·2%).



A, Periodate consumed; *B*, formic acid produced.

Hydrolysis of the glycoside with ethanolic hydrochloric acid (10%) for 3 hr. at 100° afforded solasodine, m. p. and mixed m. p. 201—202°*, and paper chromatography of the neutralised sugar solution showed the presence of glucose and rhamnose.

Examination of the Green Berries of S. aviculare.—Extraction of fresh green berries collected in Auckland in February gave solasonine (0·75%) which crystallised from aqueous methanol as colourless rectangular plates, m. p. 300—301°* (decomp.) (lit.,[7] 284—285°) (Found: C, 61·1; 61·1, 61·25; H, 8·4, 8·4, 8·4. Calc. for $C_{45}H_{73}O_{15}N$: C, 61·1; H, 8·3%). The picrate formed yellow plates, m. p. 203°* (decomp.) (lit.,[7] m. p. 200·5—201°) (Found: C, 55·4; H, 6·8; N, 5·2. Calc. for $C_{45}H_{73}O_{15},C_6H_3O_7N_3$: C, 55·0; H, 6·9; N, 5·0%). The picrolonate formed yellow plates, m. p. 234°* (decomp.) (lit.,[7] m. p. 231°) (Found: C, 57·7; H, 7·0; N, 5·8. Calc. for $C_{45}H_{73}O_{15}N,C_{10}H_8O_5N_4$: C, 57·5; H, 7·1; N, 6·1%). The infrared spectrum could not be distinguished from that of solasodamine.

Examination of the Green Berries of S. tuberosum.—Extraction of fresh green berries of *S. tuberosum* var. "Chippewa" ("potato apples") collected at Ashburton in January, and separation from considerable inorganic material containing aluminium compounds, gave solanine as colourless needles, m. p. 290°* (decomp.) (lit.,[8] m. p. 285°) (Found: C, 62·2, 62·5; H, 8·3, 8·4; N, 1·5. Calc. for $C_{45}H_{75}O_{15}N$: C, 62·3; H, 8·5; N, 1·6%). The infrared spectrum (KBr) had bands at 3448, 2985, 1460, 1437, 1422, 1370, 1346(i), 1323, 1241, 1202, 1147, 1080, 990(i), 916, 989(i), 826, 777, and 738(i) cm.$^{-1}$.

We are greatly indebted to Dr. H. Bloom for pK_b measurements, Dr. L. D. Calvert for *X*-ray powder photographs, and Dr. B. Cleverly and Mr. L. D. Colebrook for infrared measurements. We gratefully acknowledge financial assistance from the Chemical Society, The Rockefeller Foundation of New York, the Australian and New Zealand Association for the Advancement of Science, the Royal Society of New Zealand, and the Grants Committee of the University of New Zealand, and gifts of chemicals from Messrs. Rohm and Haas Company, Philadelphia. One of us (E. G. B.) is also indebted for a University Research Fund Fellowship.

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[4] Bloom and Briggs, *J.*, 1952, 3591.
[5] Briggs and Vining, *J.*, 1953, 2809.
[6] Briggs and Brooker, *J.*, 1953, 2833.
[7] Bell and Briggs, *J.*, 1942, 1.
[8] Soltys and Wallenfels, *Ber.*, 1936, **69**, 811.

XUM

285. Solanum *Alkaloids. Part XIII.** *The Examination of the Alkaloids from Seven* Solanum *Species.*

By Lindsay H. Briggs and R. C. Cambie.

The glycosidic alkaloids of the fruit of *S. laciniatum* Ait., *S. nodiflorum* Jacq. (forms A and B), *S. miniatum* Bernh., *S.* " *simile*," *S. gracile* Otto, *S. douglasii* Dun., and *S. nigrum* L. have been examined. Solasonine has been isolated from the first four species and solamargine from the others.

The morellae-verae species, *Solanum nodiflorum* Jacq. (forms A and B), *S. gracile* Otto, *S. douglasii* Dun., *S. miniatum* Bernh., and *S. nigrum* L. have often been placed together under the name *S. nigrum* L. and the dulcamara species, *S. aviculare* Forst., *S.* " *simile*," and *S. laciniatum* Ait., under the name *S. aviculare* Forst. It has been shown, however, that each is a separate species and, with the exception of *S. nodiflorum* (Forms A and B), they do not interbreed freely.[1]

The first member of the Solanum genus to be examined chemically appears to have been *S. nigrum*.[2] Desfosses[3] obtained an alkaloid from this plant which he named " solanine " and later Schutte[4] stated that this alkaloid appeared to be identical with the base contained in *S. tuberosum*. This latter alkaloid is now known to be solanine.[5] Various reports mention the " solanine " content of *S. nigrum*[6,7,8] in connection with its use in pharmacology or agriculture. In a comprehensive survey of the species of the family Solanaceae which have been reported to contain glycosidic alkaloids,[2] Schreiber has stated that the occurrence of solanine, which is often mentioned in the earlier literature, is doubtful and its presence should be verified by further investigation. This is the case with

Species	Somatic chromosome no.	Natural distribn.	Status in N.Z.	Seed source of Dunedin crop	Remarks	Yield (%) of alkaloid
Section: morellae-verae						Solasonine
S. nodiflorum Jacq. form A.	24	U.S.A.	Weed of cultivation	Berkeley, California	Form with purplish leaves but white flowers	0·30
,, form B.	24	Tropics and subtropics	Possibly indigenous	Fanal Is., Hauraki Gulf	The type form of the species; no purple pigment except at nodes; interbreeds freely with form A.	0·45
						Solamargine
S. gracile Otto	24	Unknown	Naturalised in Westland	F1 hybrids between Westland race and a race from C. E. Jorgensen, Copenhagen	Close to the Californian *S. douglasii* in appearance but genetically isolated from it	0·23
S. douglasii Dun.	24	California	Not present	Carpinteria, California	—	0·20
S. miniatum Bernh.	48	Eurasia	Not present	Portugal	—	0·10
S. nigrum L.	72	Eurasia	Extensively naturalised	F1 hybrids between a Portuguese race and one from Three Kings Is.	Species most likely to be used by chemical workers in temperate countries except U.S.A. where it is said to be still rare	0·07
Section: dulcamara						Solasonine
S. aviculare Forst.	46	N.Z., Australia	Indigenous	Narromine, N.S.W.	—	0·74
"*S. simile*"	92	W. Australia	Not present	Garden Is., Freemantle	Will have to be re-named	0·41
S. laciniatum Ait. Bernh.	92	N.Z., Australia	Indigenous	Dunedin	—	0·88

* Part XII, preceding paper.

[1] Professor G. T. S. Baylis (University of Otago, Dunedin, N.Z.), *Trans. Roy. Soc., N.Z.*, 1954, **82**, 639 and personal communication. His remarks appear in Table 1.

[2] Schreiber, *Chem. Tech. (Berlin)*, 1954, **6**, 648.

[3] Desfosses, *Jahresb.*, 1820, **2**, 114; *Pharm. J.*, 1821, **7**, 414.

[4] Schutte, *Arch. Pharm.*, 1891, **229**, 527.

[5] Prelog and Jeger, " The Chemistry of Solanum and Veratrum Alkaloids," in Manske and Holmes, " The Alkaloids," Academic Press Inc., New York, 1953, Vol. III, p. 248.

[6] Pollacci and Galotti, *Boll. Soc. ital. Biol. sper.*, 1940, **15**, 328; *Chim. et Ind.*, 1940, **44**, 528; *Chem. Abs.*, 1943, **37**, 2875.

[7] Leclerc, *Presse med.*, 1938, **46**, 480; *Chem. Abs.*, 1938, **32**, 5924.

[8] Brieg, *Suddeut. Apoth.-Ztg.*, 1940, **80**, 501; *Chem. Abs.*, 1941, **35**, 2273.

S. nigrum, the alkaloid in which has now been shown to be solamargine, and not solanine as previously believed. Solamargine was also isolated from *S. gracile* and *S. douglasii*, which differ morphologically only in two minor features [1] but are maintained as distinct species because they interbreed only with difficulty.

The fruit of *S. aviculare* has been examined by Bell and Briggs [9] and found to contain solasonine and more recently Kuhn and his co-workers [10] have shown that the leaves of the plant contain the same alkaloid and a further alkaloid corresponding to solamargine. When extracting the berries of *S. auriculatum*, *S. sodomaeum*, and *S. marginatum* by an improved method, Briggs and Brooker [11] isolated solasodamine, a glycosidic alkaloid containing a tetrasaccharide moiety, while *S. aviculare* under the same conditions gave only solasonine.

The berries * of the species now examined were extracted by the improved method of Briggs and Brooker [11] in which the possibility of enzymic hydrolysis has been minimised. Solasonine was isolated from *S. laciniatum*, *S. nodiflorum* forms A and B, *S. miniatum*, *S.* "*simile*," and again from *S. aviculare*.

In their examination of the leaves of *S. aviculare*, Kuhn and his co-workers [10] were able to separate solasonine and solamargine by chromatography, on alumina, of the total alkaloid mixture with water-saturated butan-1-ol. For good recovery from the columns it was necessary to stir and store the alumina with moist butanol before packing it. Elution with the same solvent gave solasonine and, then in higher yield, solamargine. In the present investigation, chromatography of the partially purified alkaloid material, under these conditions, gave only a single alkaloid in each of two cases tried (*viz.*, *S. laciniatum* and *S. gracile*). The compounds gave good analyses for solasonine and solamargine respectively. Kuhn and his co-workers were also able to separate solasonine (shown to be homogeneous by paper chromatography) from solamargine by purification from methanol without the addition of water. Solasonine is soluble with difficulty in absolute methanol but is soluble when water is present, while solamargine is freely soluble in absolute or aqueous methanol. In each case in the present investigation the total alkaloid content was either completely insoluble or completely soluble in absolute methanol and in the case of solamargine could not be crystallised from concentrations greater than 50% alcohol (cf. Briggs *et al.*[12]). From these results it appears that only a single alkaloid was present as the major component in the fruits of the present species.

In an attempt to identify possible mixtures of glycosidic alkaloids present in the fruits by paper chromatography the system of Kuhn and his co-workers [10,13] [ethyl acetate–acetic acid–water (3 : 1 : 3 v/v), upper phase with 15 vol. % of 85% ethanol] was used. Attempts, however, to separate authentic samples of solanine, solasonine, solamargine, and solasodamine failed. Moreover it was not even possible to obtain reproducible R_{as} values. Numerous modifications designed to standardise conditions met with no success and in view of the fluctuations of R_{as} values reported by Kuhn *et al.*[10] we regard the system as unsatisfactory for characterisation.

Satisfactory identification of the glycosidic alkaloids was achieved by normal analytical and degradative methods. The purified compounds were analysed and crystalline picrates and picrolonates were prepared and analysed in all cases. With one exception, *viz.*, *S. miniatum*, from which the glycosidic alkaloid was isolated in only small yield, the identity was confirmed, after complete hydrolysis, by identification of the alkamine by mixed melting points and infrared spectra and by paper chromatography of the liberated sugars under identical conditions.

* Forwarded by Professor G. T. S. Baylis (University of Otago, Dunedin, N.Z.).

[9] Bell and Briggs, *J.*, 1942, 1.
[10] Kuhn, Löw, and Trischmann, *Chem. Ber.*, 1955, **88**, 289.
[11] Briggs and Brooker, preceding paper.
[12] Briggs, Brooker, Harvey, and Odell, *J.*, 1952, 3587.
[13] Kuhn, Löw, and Trischmann, *Chem. Ber.*, 1955, **88**, 1492; 1957, **90**, 202; Kuhn and Löw, *Ann. Acad. Sci. Fennicae, Ser. A*, 1955, **2**, 488.

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Experimental

M. p.s were taken in evacuated tubes. Microanalyses are by Dr. A. D. Campbell, University of Otago, N.Z., samples being dried at 100° to constant weight. Infrared spectra were measured as KBr discs with a Beckman IR2 instrument.

S. laciniatum *Ait.—Isolation of solasonine.* Fresh green berries (466 g.) were coarsely minced and immediately extracted under reflux with boiling methanol for 2 hr. The pulp was separated from the mixture by using Celite as filter-aid, and washed well with hot methanol, and the filtrate was concentrated under reduced pressure to smaller volume under an anti-foaming device. After addition of an equal volume of water, ammonia was passed into the boiling solution, and the coagulated precipitate collected after cooling. The grey glycosidic alkaloid was reprecipitated twice, in a crystalline state, from 3% acetic acid solution with ammonia. Repeated crystallisation (charcoal) from aqueous methanol (75%) gave colourless, flat needles (4·10 g.) of solasonine, m. p. 301—302° (decomp.), with sintering at 296°. Chromatography of the partially purified material (m. p. 297—301°) in water-saturated butan-1-ol on alumina (previously stirred and kept for 1 hr. with moist butan-1-ol), and development with butan-1-ol–methanol (1 : 1), gave a single product (needles from 75% methanol), m. p. 301—302° (decomp.), identical with that purified by crystallisation alone (Found: C, 61·2; H, 8·1; N, 1·5. Calc. for $C_{45}H_{73}O_{16}N$: C, 61·1; H, 8·3; N, 1·6%).

The picrate, prepared from solasonine (100 mg.), saturated alcoholic picric acid solution (1 c.c.), and 30% alcohol (3 c.c.), after repeated crystallisation from 30% alcohol, gave yellow needles m. p. 197—198° (decomp.) (lit.,[9] m. p. 199—199·5°) (Found: C, 55·7; H, 7·0. Calc. for $C_{45}H_{73}O_{16}N,C_6H_3O_7N_3$: C, 55·0; H, 6·9; N, 5·0%).

The picrolonate, prepared from a solution of solasonine (100 mg.) and picrolonic acid (40 mg.) in 80% alcohol (3 c.c.), after repeated crystallisation from 80% alcohol, gave pale yellow needles, m. p. 233—234° (decomp.) (lit.,[9] m. p. 231°) (Found: C, 57·7; H, 7·25; N, 5·6. Calc. for $C_{45}H_{73}O_{16}N,C_{10}H_8O_5N_4$: C, 57·5; H, 7·1; N, 6·1%).

Hydrolysis of Solasonine.—Solasonine (500 mg.) in ethanol (10 c.c.) was hydrolysed by refluxing concentrated hydrochloric acid (2 c.c.) for 3 hr. The crystalline hydrochloride (slender needles) deposited after hydrolysis for 30 min. was collected after cooling overnight and was washed with water (10 c.c.). Treatment of a suspension of the hydrochloride with concentrated ammonia (25 c.c.) for 1 hr. at 100° gave the crude aglycone. Three crystallisations from methanol yielded large colourless hexagonal plates of solasodine, m. p. and mixed m. p. 196—198°. The infrared spectrum was identical with that of authentic solasodine.

Concentration of the hydrolysis filtrate and washings, *in vacuo*, to suitable volume and examination by paper strip chromatography with butan-1-ol–pyridine–water (3 : 1 : 1) on Whatmann No. 1 paper showed the presence of galactose, glucose, and rhamnose (aniline hydrogen phthalate spray reagent).

S. nodiflorum *Jacq. Form A.—Isolation of solasonine.* Coarsely minced fresh green berries (500 g.), on extraction, gave colourless flat needles of solasonine (1·48 g.), m. p. 297—298° (decomp.), with sintering at 296° (Found: C, 61·7; H, 8·4; N, 1·5%). The picrate formed fine yellow needles, m. p. 199—200° (decomp.) (Found: C, 55·2; H, 6·8%). The picrolonate formed pale yellow needles, m. p. 231—232° (decomp.) (Found: C, 57·9; H, 6·9; N, 6·0%).

Hydrolysis of the purified glycoside gave solasodine, m. p. and mixed m. p. 197·5—198°. The infrared spectrum was identical with that of authentic solasodine. Paper chromatography of the concentrated sugar solution showed the presence of galactose, glucose, and rhamnose.

S. nodiflorum *Jacq. Form B.—Isolation of solasonine.* Fresh green berries (178 g.), on extraction, gave solasonine (0·80 g.), m. p. 301—302° (decomp.) (Found: C, 61·6; H, 8·25; N, 1·6%) [picrate, needles, m. p. 197—199° (decomp.) (Found: C, 54·9; H, 6·75%); picrolonate, needles, m. p. 233—234° (decomp.) (Found: C, 57·4; H, 7·0; N, 5·5%)].

Hydrolysis and spectrum were as for form A.

" S. simile."—*Isolation of solasonine.* Fresh green berries (467 g.), on extraction, gave solasonine (1·93 g.), m. p. 302—303° (decomp.), with sintering at 297° (Found: C, 61·1; H, 8·0; N, 1·5%) [picrate, needles, m. p. 199—200° (decomp.) (Found: C, 54·85; H, 6·6; N, 5·2%); picrolonate, needles, m. p. 234—235° (decomp.) (Found: C, 57·2; H, 6·8; N, 5·8%)]. Further identification was as above.

S. miniatum *Bernh.—Isolation of solasonine.* Fresh green berries (144 g.) collected in March, gave on extraction solasonine (142 mg.), m. p. 302—303° (decomp.) with sintering

at 296° (Found: C, 61·2; H, 8·2; N, 1·7%) [picrate, needles, m. p. 198—199° (decomp.) (Found: C, 55·4; H, 7·1; N, 5·0%); picrolonate, needles, m. p. 234° (decomp.) (Found: C, 57·4; H, 7·1; N, 5·2%)]. Insufficient glycosidic alkaloid was isolated for hydrolysis. A second sample of *S. miniatum* berries (73 g.), collected in April, on extraction gave only a low yield (27 mg.) of alkaloid which still contained traces of inorganic material.

S. aviculare *Forst.—Isolation of solasonine.* Fresh green berries (367 g.), on extraction, gave solasonine (2·71 g.), m. p. 302—303° (decomp.), with sintering at 297° (Found: C, 61·6; H, 8·1; N, 1·6%).

S. gracile *Otto.—Isolation of solamargine.* Fresh green berries (576 g.) were extracted and worked up in the usual manner. Repeated crystallisation from aqueous methanol (50%) gave rectangular colourless plates of solamargine (1·31 g.), m. p. 301—303° (decomp.) with sintering at 296°. Chromatography of the partially purified material (m. p. 301—302°) in water-saturated butan-1-ol on alumina (as above) and development with butan-1-ol–methanol (1 : 1) gave a single product (plates from 50% methanol), m. p. 301—302° (decomp.), identical with that purified by crystallisation alone (Found: C, 62·0; H, 8·3; N, 1·45. Calc. for $C_{45}H_{73}O_{15}N$: C, 62·3; H, 8·5; N, 1·6%).

The picrate, formed from its components in boiling 50% alcohol, on repeated crystallisation from 20% ethanol containing a trace of picric acid, gave yellow needles, m. p. 186—187° (decomp.) (lit.,[12] m. p. 188—189°) (Found: C, 56·3, 56·6; H, 7·4, 7·1. Calc. for $C_{45}H_{73}O_{15}N,C_6H_3O_7N_3$: C, 55·8; H, 6·9; N, 5·1%). The picrolonate, formed from its components in hot 80% ethanol, after four recrystallisations from the same solvent gave pale yellow needles, m. p. 202—203° (decomp.) (lit.,[12] m. p. 204—205°) (Found: C, 58·5; H, 7·0; N, 5·1. Calc. for $C_{45}H_{73}O_{15}N,C_{10}H_8O_5N_4$: C, 58·3; H, 7·2; N, 6·2%).

Hydrolysis of Solamargine.—Hydrolysis of the purified glycoside (500 mg.) under the usual conditions gave solasodine, m. p. and mixed m. p. 197—198°, having the authentic infrared spectrum. Paper chromatography of the concentrated sugar solution showed the presence of glucose and rhamnose.

S. douglasii *Dun.—Isolation of solamargine.* Fresh green berries (279 g.), on extraction, gave solamargine (548 mg.), m. p. 304—305° (decomp.) with sintering at 296° (Found: C, 62·4; H, 8·6; N, 1·7%) [picrate, needles, m. p. 186—187° (decomp.) (Found: C, 56·4; H, 6·85; N, 4·4%); picrolonate, needles, m. p. 200—201° (decomp.) (Found: C, 58·8; H, 7·5; N, 5·6%)].

Hydrolysis of the purified glycoside (100 mg.) gave solasodine, m. p. and mixed m. p. 199—200°, having the authentic infrared spectrum. Paper chromatography of the concentrated sugar solution showed the presence of glucose and rhamnose.

S. nigrum *L.—Isolation of solamargine* (in part B. R. Davis). Fresh green berries (320 g.), on extraction, gave solamargine (220 mg.), m. p. 313° (decomp.), with sintering at 298° (Found: C, 62·1; H, 8·5; N, 1·5%) [picrate, needles, m. p. 187—188° (decomp.) (Found: C, 55·9; H, 6·9%); picrolonate, needles, m. p. 203—204° (decomp.) (Found: C, 58·1; H, 7·0%)], further identified as in the preceding case.

We are indebted to Professor G. T. S. Baylis for supplies of the berries. Assistance is gratefully acknowledged from the Chemical Society, the Rockefeller Foundation, The Australian and New Zealand Association for the Advancement of Science, and the Research Grants Committee of the University of New Zealand, and one of us (R. C. C.) acknowledges a University Research Fund Fellowship.

University of Auckland, Auckland, New Zealand. [*Received, November 29th,* 1957.]

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286. *The Kinetics of Alkaline Hydrolysis of Substituted Ethyl 1-Naphthoates.*

By A. Fischer, W. J. Mitchell, G. S. Ogilvie, J. Packer, J. E. Packer, and J. Vaughan.

Rates of alkaline hydrolysis, in 85% (w/w) ethanol–water, of ethyl 3- and 4-chloro-, 3-, 4-, and 5-bromo-, and 3- and 4-methyl-1-naphthoates and of ethyl 1-naphthoate have been measured within the temperature range 25—75°. The results allow an estimate to be made of the steric-hindrance effect of the fused ring in this reaction. A value for the Hammett reaction constant has been obtained from naphthoate hydrolysis alone.

Rates of alkaline hydrolysis of ethyl nitro-1-naphthoates have recently been reported.[1] We have now extended this work by kinetic studies on the esters listed above.

Experimental

New substituted 1-naphthoic acids were prepared as follows:

3-Chloro-1-naphthoic Acid.—*N-Acetyl-4-bromo-2-chloro-1-naphthylamine.* Chlorine was bubbled through a suspension of *N*-acetyl-4-bromo-1-naphthylamine [2] (165 g.) in glacial acetic acid (1 l.) at room temperature for 2 hr. The solid was filtered off, and water added to the filtrate. The resulting precipitate was recrystallised (charcoal) from ethanol, and then combined with the residue from the first filtration before being recrystallised twice from ethanol. The *N-acetyl-4-bromo-2-chloro-1-naphthylamine* was obtained as colourless crystals (125 g., 67%), m. p. 231° (Found: C, 48·5; H, 3·0; N, 4·6. $C_{12}H_9ONClBr$ requires C, 48·3; H, 3·0; N, 4·7%).

4-Bromo-2-chloro-1-naphthylamine. The naphthalide (125 g.) was refluxed with a mixture of ethanol (750 ml.), water (450 ml.) and concentrated sulphuric acid (300 ml.) until all the solid disappeared (*ca.* 6 hr.). The solution was poured into water, and the precipitate separated by filtration and recrystallised (charcoal) three times from acetic acid. *4-Bromo-2-chloro-1-naphthylamine* (77 g., 71%) was obtained, m. p. 113° (Found: C, 46·7; H, 2·9; N, 5·4. $C_{10}H_7NClBr$ requires C, 46·8; H, 2·7; N, 5·5%).

1-Bromo-3-chloronaphthalene. The foregoing amine (20 g.), dissolved in acetic acid (125 ml.), was added to a stirred, freshly prepared solution of sodium nitrite (7 g.) in concentrated sulphuric acid (45 ml.) below 20°. Stirring was continued for 30 min., and the mixture was then added during 30 min. to a stirred suspension of cuprous oxide (21 g.) in ethanol (180 ml.). After evolution of nitrogen had ceased the mixture was filtered, and the residue washed with boiling ethanol (100 ml.). The combined filtrate and washings were poured into water, and the precipitate recrystallised (charcoal) from methanol containing a little acetone to give crude 1-bromo-3-chloronaphthalene, m. p. 56·5°. The coloured impurities were removed by passing a solution of the product in hexane (100 ml.) through a short alumina column. Removal of the solvent and recrystallisation of the product from methanol–acetone yielded the compound as colourless crystals (13·5 g., 70%), m. p. 56·5°. This compound had previously been prepared [3] in unstated yield from 3-chloro-1-naphthylamine, itself obtained by a laborious process.

3-Chloro-1-naphthoic acid. 1-Bromo-3-chloronaphthalene (24·2 g., 0·1 mole) in ether (50 ml.) was added to a solution of *n*-butyl-lithium (0·1 mole) in ether (96 ml.) at −35°. After vigorous shaking at −35° for 10 min. the mixture was stirred into a slurry of solid carbon dioxide and ether. Isolation by the usual method [4] gave the crude *acid*, m. p. 218—221°. After three recrystallisations from aqueous ethanol and one from aqueous acetic acid it was obtained (8·9 g., 43%) as colourless crystals, m. p. 223° (Found: Cl, 17·3%; equiv., 206·6. $C_{11}H_7O_2Cl$ requires Cl, 17·2%; equiv., 206·5).

3-Methyl-1-naphthoic Acid.—*4-Bromo-2-methyl-1-naphthylamine.* Bromine (8 ml.) in carbon

[1] Fischer, Murdoch, Packer, Topsom, and Vaughan, *J.*, 1957, 4358.
[2] Hodgson and Birtwell, *J.*, 1943, 321.
[3] Hodgson and Hathway, *J.*, 1944, 538.
[4] Hussey, *J. Amer. Chem. Soc.*, 1951, **73**, 1364.

tetrachloride (40 ml.) was added with stirring at −5° to a solution of 2-methyl-1-naphthylamine [5] (23 g.) in carbon tetrachloride containing iodine and iron powder. After 10 minutes' stirring the precipitated amine hydrobromide was filtered off and dried under vacuum; when it was dissolved in hot ethanol and poured into aqueous sodium hydrogen carbonate, crude 4-bromo-2-methyl-1-naphthylamine (m. p. 68—74°) was obtained. Three recrystallisations from light petroleum (b. p. 50—70°) gave 4-bromo-2-methyl-1-naphthylamine (11 g., 31%), m. p. 78°. (If the *crude* product was heated in a solvent above 65° a tar was formed.) This amine has been prepared in very low yield by hydrolysis of *N*-acetyl-4-bromo-2-methyl-1-naphthylamine.[6]

1-*Bromo*-3-*methylnaphthalene*. 4-Bromo-2-methyl-1-naphthylamine was deaminated by the method described for 4-bromo-2-chloro-1-naphthylamine. The resulting mixture was steam-distilled. After ether extraction of the distillate and removal of ether from the extracts, the yellow, oily residue was distilled in vacuum to yield 1-bromo-3-methylnaphthalene (48%), b. p. 127°/3·5 mm. This preparation is simpler than that due to Veselý.[7]

3-*Methyl*-1-*naphthoic acid*. *n*-Butyl-lithium (0·025 mole) in ether (25 ml.) was added at room temperature to 1-bromo-3-methylnaphthalene (5·6 g., 0·025 mole) in ether (75 ml.). The mixture was shaken for 30 sec. and then stirred into a slurry of solid carbon dioxide and ether. After excess of carbon dioxide had evaporated, hydrochloric acid and ethanol were added and the ether was distilled off. On cooling, crude 3-*methyl*-1-*naphthoic acid* was obtained, m. p. 168—172°. Four recrystallisations from aqueous ethanol gave colourless crystals (3 g., 64%), m. p. 173·5° (Found: C, 77·4; H, 5·2%; equiv., 186·0. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%; equiv., 186·2).

Of the known acids, 1-naphthoic acid had m. p. 160° and 4-methyl-1-naphthoic acid,[8] m. p. 174°. 4-Chloro-1-naphthoic acid (m. p. 225°; yield 57%) and 4-bromo-1-naphthoic acid (m. p. 221°; yield 80%) were prepared, by the method described for 3-chloro-1-naphthoic acid, from 1-bromo-4-chloronaphthalene [9] (6 g.) and 1 : 4-dibromonaphthalene [10] (14 g.) respectively. 3-Bromo-1-naphthoic acid (m. p. 236°; yield 50%) was prepared from 3-nitro-1-naphthoic acid [11] through reduction to the amine sulphate [12] (not isolated) followed by diazotisation and subsequent formation of the diazonium mercuribromide, which was decomposed to the required acid by heating at 110° with sodium bromide (cf. ref. 13).

Esters.—These were all prepared by the Fischer–Speier method. Physical constants, etc., were as follows: Ethyl 1-naphthoate, b. p. 116°/1 mm.; ethyl 3-methyl-1-naphthoate, b. p. 155°/2 mm.; ethyl 4-methyl-1-naphthoate, b. p. 172°/4·5 mm.; ethyl 4-bromo-1-naphthoate, m. p. 43·5°; ethyl 5-bromo-1-naphthoate, m. p. 48°; ethyl 4-chloro-1-naphthoate, m. p. 27·5°; *ethyl* 3-*chloro*-1-*naphthoate*, b. p. 133°/0·75 mm. (Found: Cl, 15·1. $C_{13}H_{11}O_2Cl$ requires Cl, 15·1%); *ethyl* 3-*bromo*-1-*naphthoate*, needles from aqueous alcohol, m. p. 28° (Found: Br, 28·1. $C_{13}H_{11}O_2Br$ requires Br, 28·6%).

Hydrolyses.—The purification of solvent ethanol and of reagents has been described, as has the general titration method of following kinetics.[1] At temperatures above 55°, corrections were required for alkaline attack on the glass wall of the reaction vessel; these were obtained from blank runs, with ester omitted. For ethyl 3- and 4-bromonaphthoates, use of stainless-steel reaction vessels eliminated the blank. Rate constants for these two esters are fully comparable with those for the other esters; rate constants for ethyl 1-naphthoate measured by both techniques were in good agreement (see Table 1).

For each ester, runs were carried out at four temperatures, good second-order kinetics being obtained. Runs with unequal concentrations of ester and base showed that reactions were of first order with respect to each reactant. Good Arrhenius plots of $\log k$ *versus* $1/T$ were obtained. Rate constants and Arrhenius parameters (in $\log k = \log B - E/RT$) are given in Table 1. The probable error in each of these parameters is *ca.* 0·1 in every case. For ethyl naphthoate three sets of results, obtained by three different individuals, are given.

[5] Adams and Albert, *J. Amer. Chem. Soc.*, 1942, **64**, 1476.
[6] Shoesmith and Rubli, *J.*, 1927, 3103.
[7] Veselý and Kapp, *Rec. Trav. chim.*, 1925, **44**, 360.
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[9] Fieser and Desreux, *J. Amer. Chem. Soc.*, 1938, **60**, 2261.
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[11] Leuck, Perkins, and Whitmore, *J. Amer. Chem. Soc.*, 1929, **51**, 1831.
[12] Jacobs and Gould, *J. Biol. Chem.*, 1937, **120**, 141.
[13] Newman and Wise, *J. Amer. Chem. Soc.*, 1941, **63**, 2847.

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Results in the first two rows of Table 1 were derived from runs in glass reaction flasks. The third set of results was obtained by using stainless steel reaction vessels.

TABLE 1. *Rates of hydrolysis* (10^3k, with k in l. mole^{-1} sec.$^{-1}$) *of ethyl* X-1-*naphthoates at various temperatures.*

X	25°	35°	45°	55°	65°	75°	E *	log B
H	—	0·704, 0·718	1·67, 1·72 1·74	3·67, 3·82 3·84	—	—	16·7	8·7
H	—	—	1·51, 1·53 1·56	3·53, 3·61 3·68	7·76, 7·79 7·88	16·0, 16·0	17·2	9·0
H	0·240, 0·241 0·242	0·716, 0·719	—	3·40, 3·43 3·45, 3·45	8·07, 8·07 8·12, 8·12	—	17·3	9·1
3-Cl	2·01, 2·09 2·14	5·04, 5·06 5·13	11·1, 11·2 11·3, 11·4	25·5, 25·6	—	—	16·1	9·1
4-Cl	—	2·45, 2·45	6·02, 6·02 6·05	13·2, 13·2	30·3, 30·5	—	17·2	9·6
3-Br	2·10, 2·13 2·16	—	11·2, 11·3 11·3	—	49·6, 52·0 52·4	—	15·8	8·9
4-Br	1·04, 1·05	2·72, 2·77 2·83	—	13·2, 13·3 13·3, 13·5	31·6, 31·8 32·0	—	16·7	9·3
5-Br	1·04, 1·04 1·05	—	5·45, 5·57 5·57	12·6, 12·7	25·6, 25·9 25·9	—	16·2	8·9
3-CH_3	—	—	1·13, 1·16 1·17	2·71, 2·71	6·05, 6·15 6·24	12·8, 12·9 13·1	17·8	9·3
4-CH_3	—	—	0·750, 0·750 0·754	1·69, 1·69 1·72	3·90, 3·90 3·95	8·65, 8·80 8·86	18·1	9·3

* In kcal. mole^{-1}.

DISCUSSION

It has already been shown [1] that, within experimental error, the alkaline hydrolyses of ethyl 1-naphthoate and of ethyl 3-, 4-, 5-, and 6-nitro-1-naphthoate are isoentropic (log B is constant). This conclusion can now be extended to include the hydrolyses of ethyl 3- and 4-chloro-, 3-, 4-, and 5-bromo-, and 3- and 4-methyl-1-naphthoates. These extensive results suggest that for the alkaline hydrolyses of all simple 3-, 4-, 5-, 6-, and 7-substituted 1-naphthoates, log B is likely to be constant. In such substituted naphthoates the substituents should be held rigidly at relatively large distances from the reaction centre. Thus, as in the *meta*- and *para*-substituted benzoates, there should be negligible steric interference, by the substituent, with the approach of the attacking hydroxide ion.

The mean of 14 values for log B obtained from the alkaline hydrolysis of *meta*- and *para*-substituted ethyl benzoates [14,15] in 85% ethanol is 9·7 with a probable error of ±0·02. The mean of the 14 values of log B, obtained from the similar hydrolysis of the specific naphthoates listed above, is 9·3 ± 0·07. The difference, which is equivalent to 0·65 kcal. mole^{-1} in $T\Delta\Delta S^{\ddagger}_{50°}$, is a measure of the steric hindrance of a 2 : 3-benzo-substituent in this reaction.* This measure of steric hindrance is sufficient to explain the difference in rate of hydrolysis of a *meta*- or *para*-substituted ethyl benzoate and a corresponding naphthoate. In Table 2 are listed, for correspondingly substituted ethyl benzoates and naphthoates, values of $-\boldsymbol{RT}\ln k_{50°}$ and values of the relative free energy of activation, $\Delta\Delta G^{\ddagger}_{50°}$, *i.e.*,

$$\Delta G^{\ddagger}_{\text{naphthoate}} - \Delta G^{\ddagger}_{\text{benzoate}} = -\boldsymbol{RT}\ln k_{50°,\text{ naphthoates}} + \boldsymbol{RT}\ln k_{50°,\text{ benzoates}}$$

Data for the 4-nitro-substituent, although available, are not included in this Table because of the demonstrated complication of steric inhibition of resonance in a 4-nitronaphthoate.[1] Values of $\Delta\Delta G^{\ddagger}_{50°}$ given in Table 2 are constant within experimental error. In the case of

* This value compares with a value of 0·6 kcal. mole^{-1} otherwise determined in these laboratories.[16]

[14] Ingold and Nathan, *J.*, 1936, 222.
[15] Evans, Gordon, and Watson, *J.*, 1937, 1430.
[16] Wong, Thesis, University of New Zealand, 1957.

the 3-nitro-substituent, an extrapolation, from published data at 25° and 35° only, was required to obtain log $k_{50°}$. The resultant uncertainty in this value is probably reflected in the rather large deviation, from the mean, of $\Delta\Delta G^{\ddagger}_{50°}$ for this substituent. The mean value of $\Delta\Delta G^{\ddagger}_{50°}$ is 0·61 kcal. mole^{-1}. Within experimental error this is equal to the $T\Delta\Delta S^{\ddagger}_{50°}$ value of 0·65 kcal. mole^{-1}. Thus the relative heat of activation, $\Delta\Delta H^{\ddagger}$, for

TABLE 2.

Substituent	H	3-NO_2	3-Cl	4-Cl	4-Br	3-CH_3	4-CH_3
$-RT \ln k_{50°,\text{benzoate}}$	3·30	0·73	2·07	2·47	2·35	3·46	3·80
$-RT \ln k_{50°,\text{naphthoate}}$	3·88	1·52	2·62	3·03	2·99	4·07	4·37
$\Delta\Delta G^{\ddagger}$	0·58	0·79	0·55	0·56	0·64	0·61	0·57

corresponding benzoates and naphthoates, is negligible. This, of course, does not mean that the 2 : 3-benzo-substituent has no polar, steric strain, or " resonance " effect [17] but rather that the algebraic sum of these effects is approximately zero. Sufficient data are now available to allow accurate evaluation of the Hammett reaction constant ρ for the alkaline hydrolysis of the ethyl 1-naphthoate series. By Jaffé's method,[18] two regression lines were fitted to the log $k_{50°}$ *versus* σ (Hammett substituent constant) data from Table 3. In this table values of log $k_{50°}$ were derived from the Arrhenius relationship fitted to the data in Table 1. Values for σ are those of Jaffé.

The value of $\rho_{50°}$ so obtained is 2·21, the correlation coefficient r is 0·998, the calculated log k_0 value is 2·59, and the slope of second regression line is 0·451. New σ values are

TABLE 3.

Substituent	H	H	H	3-NO_2	3-Cl	4-Cl	3-Br
$-\log k_{50°}$	2·59	2·62	2·64	1·03	1·77	2·05	1·77
σ	0·000	0·000	0·000	0·710	0·373	0·227	0·391
σ_n	—	—	—	0·706	0·372	0·246	0·372
Substituent	4-Br	3-CH_3	4-CH_3	4-NO_2	5-NO_2	6-NO_2	5-Br
$-\log k_{50°}$	2·02	2·75	2·95	0·99	1·46	1·51	2·07
σ	0·232	−0·069	−0·170	0·778	—	—	—
σ_n	0·259	−0·070	−0·160	0·724	0·512	0·489	0·236

given by the expression * $\sigma_n = 1{\cdot}170 + 0{\cdot}451 \log k_{50°}$. By using the experimental log k_{50} data in the latter expression, σ_n values were computed and are tabulated in the third line of Table 3. For the reason mentioned above the data for the 4-nitro-substituent were not used in determining the regression lines.

For alkaline hydrolysis of ethyl 1-naphthoates in 85% ethanol, $\rho_{50°}$ is slightly smaller than $\rho_{50°}$ for similar hydrolysis of ethyl benzoates,[18] *viz.*, 2·21 as compared with 2·32. The difference between the values is small and, without data on other reaction series, it is doubtful whether this difference is significant. It has been concluded,[1] from similar rate data on 3- and 4-nitro-benzoates and -naphthoates, that the same hydrolytic mechanism ($B_{AC}2$) applies to both aromatic series. The close similarity in ρ values confirms this conclusion.

The data in Table 3 show that the 5-bromo-substituent has a σ_n value not very different from that of the 4-bromo-substituent ($\sigma_4 - \sigma_5 = 0{\cdot}023$). For the nitro-substituent, however, a change from position 4 to position 5 results in a much greater decrease ($\sigma_4 - \sigma_5 = 0{\cdot}212$) in σ_n. In position 5, both I and T effects of a substituent are expected to be smaller than in position 4. In the case of the bromo-substituent it appears that the decrease in

* The subscript n (= naphthalene) merely denotes the different origin of the substituent constant in this expression. Its purpose is only to simplify present comparison of σ values, obtained from studies in the benzene series, with corresponding values derived from the naphthalene series.

[17] Taft, in Newman, " Steric Effects in Organic Chemistry," John Wiley and Sons Inc., New York, 1956.

[18] Jaffé, *Chem. Rev.*, 1953, **53**, 191.

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magnitude of its $-I$ effect is almost fully compensated by the reduction in its $+M$ effect. With the nitro-substituent, on the other hand, the reductions in its $-I$ and $-T$ effects are cumulative.

The authors thank the Research Fund Committee of the University of New Zealand for a grant.

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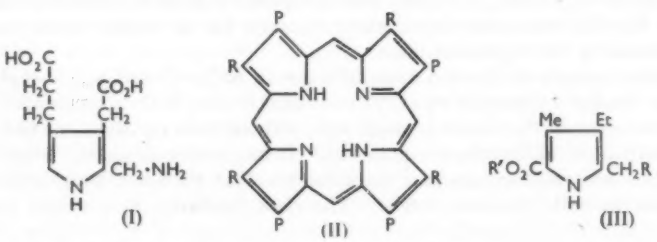
287. *A Synthesis of Coproporphyrin III.*

By E. BULLOCK, A. W. JOHNSON, E. MARKHAM, and K. B. SHAW.

Coproporphyrin III tetraethyl ester has been obtained by the action of glacial acetic acid on 5-acetoxymethyl-4-2′-ethoxycarbonylethyl-3-methylpyrrole-2-carboxylic acid, followed by aerial oxidation. A mechanism is suggested for the polymerisations of 2-(α-substituted methyl)pyrroles to III-type porphyrins, which includes the biological polymerisations of porphobilinogen. A modified Knorr synthesis is employed for the preparation of certain of the pyrrole intermediates.

BIOGENETIC studies in the porphyrin series have established[1] that the immediate precursor of the porphyrin ring is porphobilinogen (I), itself obtained by the self-condensation of δ-aminolævulic acid. Porphobilinogen, which is the biological precursor of both hæmin and chlorophyll, can be converted into uroporphyrin III (II; R = $CH_2{\cdot}CO_2H$; P = $CH_2{\cdot}CH_2{\cdot}CO_2H$) both *in vitro* and *in vivo*.[2] In considering the precise mechanism of this polymerisation, we have now shown that coproporphyrin III (II; R = Me) may also be synthesised by the polymerisation of a suitably substituted pyrrole, formally related to porphobilinogen.

A relatively mild synthesis of porphyrins *in vitro* was described in 1943 by Siedel and Winkler[3] who claimed that 4-ethyl-5-hydroxymethyl-3-methylpyrrole-2-carboxylic acid (III; R = OH, R′ = H) gave a mixture of ætioporphyrins I and II when heated with

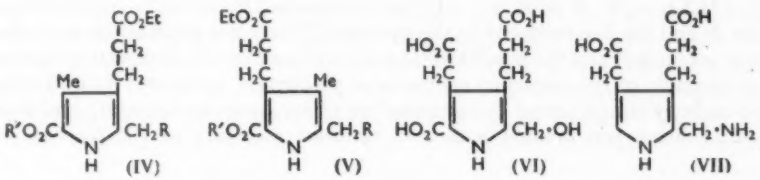


dilute hydrochloric acid. The 5-hydroxymethyl group was obtained by elaboration of the corresponding 5-methyl compound; it was claimed that the action of lead tetra-acetate on the ethyl ester gave the 5-hydroxymethyl derivative (III; R = OH, R′ = Et), m. p. 126—128°, which was acetylated to the 5-acetoxymethyl compound (III; R = OAc, R′ = Et), m. p. 135—136°, and hydrolysed with alcoholic potassium hydroxide to the corresponding acid (III; R = OH, R′ = H). In common with Professor G. W. Kenner (personal communication) we have observed that the product from the lead tetra-acetate

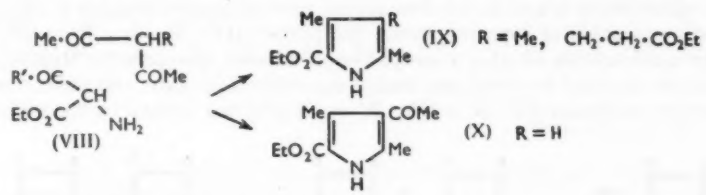
[1] Shemin and Russell, *J. Amer. Chem. Soc.*, 1953, **75**, 4873; Cookson and Rimington, *Nature*, 1953, **171**, 875; *Biochem. J.*, 1954, **57**, 476; Westall, *Nature*, 1952, **170**, 614.
[2] Dresel and Falk, *Biochem. J.*, 1956, **63**, 80.

reaction is in fact the 5-acetoxymethyl compound (III; R = OAc, R′ = Et) as would be expected. It is unchanged by acetic anhydride but is readily converted into the 5-ethoxymethyl analogue (III; R = OEt, R′ = Et) when heated in ethanol for a short time. It is thus most unlikely that Siedel and Winkler's starting product had the structure claimed for it. The German authors also carried out similar reactions in the coproporphyrin series, but their product was not purified although it was thought to contain coproporphyrin I; however, by analogy with the experiments in the ætioporphyrin series it is probable that once again their starting material did not have the structure (IV; R = OH, R′ = H) claimed for it.

As a reliable method for distinguishing the ætioporphyrin isomers is lacking, we selected the coproporphyrin series, as the simplest in which the various isomers can be recognised,



in order to define the experimental conditions necessary to bring about the apparent "reversal" of ring D leading to the formation of III-type porphyrins. The requisite pyrrole intermediates for coproporphyrin were (IV; R = OAc, R′ = CH_2Ph) and (V; R = OAc, R′ = CH_2Ph), the ester groups being used to facilitate the synthesis of the intermediates and to prevent premature porphyrin formation. Moreover, the benzyl (or *tert.*-butyl) esters were preferred as conversion into the corresponding acids avoided the application of extremes of pH. There is evidence in the literature to suggest that the position of the α-acetoxymethyl group (or its equivalent) relative to the β-substituents is immaterial [as in (IV) and (V)] in this method of synthesis of III-type porphyrins; thus Treibs and



Ott [4] have prepared (although experimental details are still lacking) uroporphyrin III (since stated to be impure [5]) from the acid (VI) which is equivalent to *iso*porphobilinogen [6] (VII); and Fischer, Sturm, and Friedrich [7] have obtained coproporphyrin III (and I) from the ester (IV; R = Br, R′ = Et) by the action of hydrogen bromide under vigorous conditions.

The pyrrole (IV; R = OAc, R′ = CH_2Ph) was prepared by the action of lead tetra-acetate on the ester (IV; R = H, R′ = CH_2Ph), itself obtained by a variation related to those of Kleinspehn [8] and Fischer and Fink [9] of the well-known Knorr synthesis. Condensation of α-aminoacetoacetic esters (VIII; R′ = Me) with 3-alkylpentane-2 : 4-diones is now

[3] Siedel and Winkler, *Annalen*, 1943, **554**, 165.
[4] Treibs and Ott, *Naturwiss.*, 1953, **40**, 476.
[5] MacDonald, quoted by Rimington, *Ann. Rev. Biochem.*, 1957, **26**, 562.
[6] Prasad and Raper, *Nature*, 1955, **175**, 629.
[7] Fischer, Sturm, and Friedrich, *Annalen*, 1928, **431**, 244.
[8] Kleinspehn, *J. Amer. Chem. Soc.*, 1955, **77**, 1546.
[9] Fischer and Fink, *Z. physiol. Chem.*, 1944, **280**, 123; 1948, **283**, 152.

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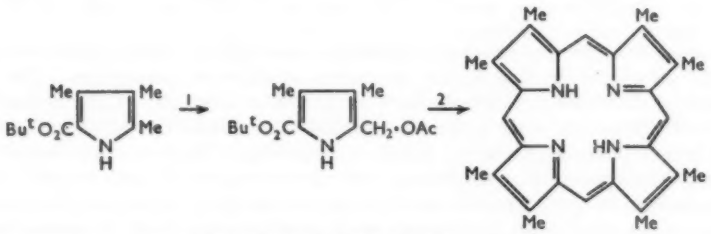
shown to yield pyrroles of type (IX), although acetylacetone itself gives (X) by a normal Knorr condensation.

The presence of the 3-alkyl substituent in pentane-2 : 4-dione decreases the ease of carbanion formation at $C_{(3)}$ and thereby completely changes the course of the condensation. Pyrroles of type (IX), which are useful intermediates for porphyrin syntheses, may thus be obtained without difficulty. In establishing the course of the above condensation, diethyl 2-amino-3-oxoadipate (VIII; R′ = $CH_2 \cdot CH_2 \cdot CO_2Et$) was substituted for ethyl α-aminoacetoacetate, in the condensation with 3-methylpentane-2 : 4-dione: the compound (IX; R = Me) was obtained, the succinoyl residue having been eliminated from the amino-ester. Similarly, condensation of diethyl 2-amino-3-oxoglutarate (VIII; R′ = $CH_2 \cdot CO_2Et$) with ethyl 4-acetyl-5-oxohexanoate gave the same pyrrole (IX; R = $CH_2 \cdot CH_2 \cdot CO_2Et$) ≡ (IV; R = H, R′ = Et) as was obtained from ethyl α-aminoacetoacetate. When the 3- and the 5-substituent in the pyrroles (IX) are not identical an unsymmetrical β-diketone is required and the possible modes of condensation are appreciably increased.

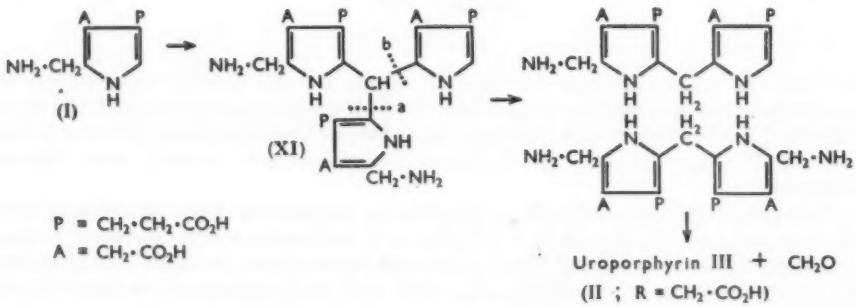
As an example of the simplified synthesis of porphyrins, *tert.*-butyl 3 : 4 : 5-trimethylpyrrole-2-carboxylate (obtained by condensation of *tert.*-butyl acetoacetate and 3-methylpentane-2 : 4-dione) was treated with lead tetra-acetate, to give the 5-acetoxymethyl



Reagents: 1, $Pb(OAc)_4$; 2, Heat.

derivative which, when heated in ethylene glycol, gave octamethylporphin in 22% yield.

For the preparation of coproporphyrin, the pyrrole (IV; R = H, R′ = CH_2Ph) was obtained by condensation of ethyl 4-acetyl-5-oxohexanoate (prepared by Michael addition of acetylacetone to ethyl acrylate) and benzyl α-aminoacetoacetate, and the corresponding acetoxymethyl compound (IV; R = OAc, R′ = CH_2Ph) was formed by the action of lead

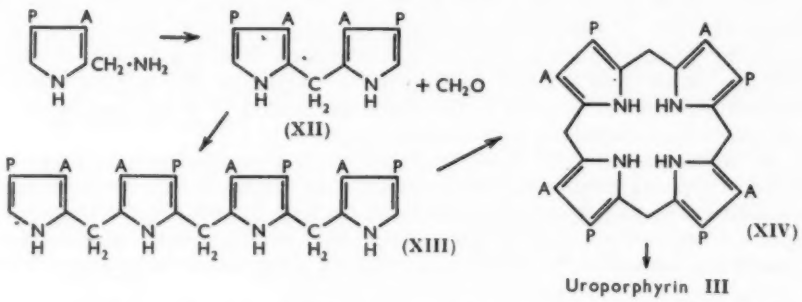


tetra-acetate. Hydrogenolysis of this ester gave the acid (IV; R = OAc, R′ = H) which, when heated under reflux with acetic acid, was rapidly transformed into a coloured condensation product from which crystalline coproporphyrin III tetraethyl ester,[10] m. p. 147—149°, was isolated. The identification of the porphyrin was confirmed by its ultraviolet

[10] Fischer and Andersag, *Annalen*, 1927, **458**, 133.

and visible absorption spectrum and by the behaviour of the corresponding free acid on chromatography.[11] Smaller yields of coproporphyrin III tetraethyl ester were obtained by heating the acetate (IV; R = OAc, R′ = H) in ethanol with dilute hydrochloric acid or by keeping it in presence of either dilute hydrochloric acid or dilute ammonia at room temperature for several days. No evidence based on paper chromatography was obtained for more than traces of the other isomers of coproporphyrin in the products obtained from any of these reactions although it is possible that a certain amount of fractionation occurred during the purification. In view of this ambiguity and the difficulty we have experienced in obtaining reproducible paper-chromatographic results even in the presence of authentic markers, further experiments are in progress.

The almost exclusive formation of coproporphyrin III in this manner is thus in line with the biogenetic formation, from porphobilinogen (I), of III-type porphyrins as well as chlorophyll,[12] and vitamin B_{12},[13] and the basic mechanism of all of these reactions, *in vitro* as well as *in vivo*, is almost certainly the same. The decarboxylation of the pyrroles (IV; R = OAc, R′ = H) and (VI) during their self-condensation occurs quite readily and requires no fundamental modification of the mechanism. Various theories[14] have been proposed to account for the wide occurrence of the III-type porphyrins in Nature; the main experimental observations to be incorporated in any such theory being the elegant work, culminating in the discovery of porphobilinogen, of Shemin and his collaborators[15] on the biosynthesis of hæmin. Shemin's theory of the mode of self-condensation of porphobilinogen is based on the synthetic studies of Corwin *et al.*,[16] and postulates an intermediate tripyrromethane (XI) which, it is argued, could break in each



of the two modes (a and b) to give two dipyrromethanes which then combine to give the porphyrin with elimination of formaldehyde.

Several objections can be raised to such a scheme: (i) Pyrroles of the porphobilinogen type have never been found to yield a tripyrromethane by condensation. (ii) The fission of tripyrromethane yields dipyrromethenes,[17] not dipyrromethanes, and usually only one isomer; the condensation of dipyrromethenes to porphyrins requires comparatively vigorous chemical conditions. (iii) There is evidence[18] to suggest that all Ehrlich-reactive

[11] Dresel and Falk, *Biochem. J.*, 1956, **63**, 87. We are extremely grateful to Professor C. Rimington, F.R.S., and to Mrs. A. Latter for confirming this result on our synthetic sample.
[12] Granick, Ciba Foundation Symposium, " Porphyrin Biosynthesis and Metabolism," London, 1955, p. 143.
[13] Shemin, Corcoran, Rosenblum, and Miller, *Science*, 1956, **124**, 272; Smith, *Chem. and Ind.*, 1957, 572.
[14] Rimington, *Ann. Rev. Biochem.*, 1957, **26**, 561; Lemberg and Legge, " Haematin Compounds and Bile Pigments," Interscience Publ. Inc., New York and London, 1949, p. 632; Maitland, *Quart. Rev.*, 1950, **4**, 45.
[15] Shemin, Ciba Foundation Symposium, " Porphyrin Biosynthesis and Metabolism," London, 1955, p. 4.
[16] Corwin, Andrews, *et al.*, *J. Amer. Chem. Soc.*, 1937, **59**, 1973; 1950, **72**, 491.
[17] Treibs, Herrmann, Meissner, and Kuhn, *Annalen*, 1957, **602**, 153.
[18] Bogorad, quoted by Granick, ref. 12, p. 146.

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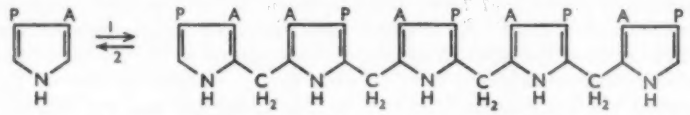
material (*i.e.*, α-free pyrroles) is removed in the reaction. (iv) Other possible modes of combination of the fragments are neglected.

Another theory due to Granick [12] meets certain of the objections but still involves

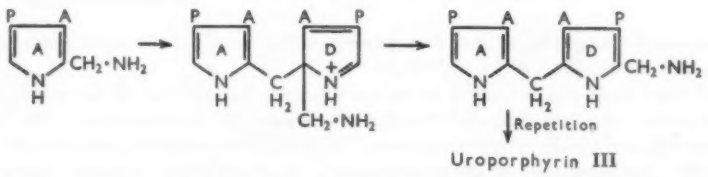


[1] + 4Porphobilinogen — $4NH_3$. [2] — Uroporphyrin III.

dipyrromethenes as break-down products. Cookson and Rimington,[19] on the other hand, avoid the tripyrromethane intermediate by postulating an initial condensation of two porphobilinogen molecules to give a symmetrical dipyrromethane (XII) and a molecule of formaldehyde by a mechanism involving carbonium ions. It is claimed that regular addition of porphobilinogen eventually gives a tetrapyrrane (XIII) which cyclises by condensation with formaldehyde (or the equivalent, *e.g.*, another molecule of porphobilinogen) to give uroporphyrinogen III (XIV) and this on oxidation yields the porphyrin.

The source of the final *meso*-bridge carbon atom is not clear although an experiment using [^{14}C]formaldehyde should determine whether in fact the condensation is intermolecular as claimed. If addition of the third and the fourth porphobilinogen unit does not proceed as illustrated, other isomers of the porphyrin will be produced and the theory offers no explanation of the very high yields of uroporphyrin III, apparently uncontaminated with other isomers, which can be formed from porphobilinogen, *e.g.*, 77% by the action of 0·5N-hydrochloric acid at 100° for 20 min.,[20] and approaching 90% under certain conditions *in vivo*.[2] A possible modification of Cookson and Rimington's scheme has been suggested by Jackson and MacDonald [21] and involves a penta- or higher poly-pyrrane. In this case, there is no evidence to support the suggestion that 4-2′-carboxyethyl-3-carboxymethylpyrrole is involved in the biogenesis or that it or the postulated pentapyrrane would react exclusively in the manner proposed.

In his Weizmann lectures,[22] Robinson suggested an intramolecular mechanism for the formation of type-III porphyrins. He suggested that the initial step involved attack of the α-substituent of one porphobilinogen molecule (corresponding to ring D of the porphyrin) at $C_{(2)}$ of a second molecule (corresponding to the porphyrin ring A) in the manner suggested by Cookson and Rimington.[19] Instead of elimination of formaldehyde, however, Robinson

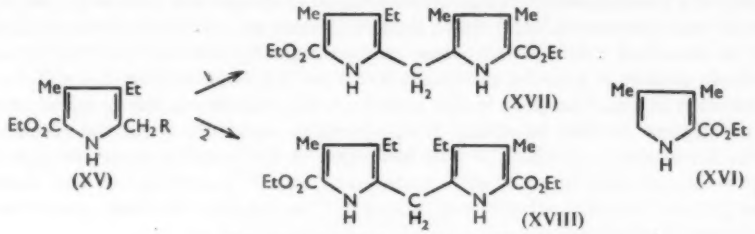


preferred to regard the aminomethyl group as migrating to the 5-position of the ring "possibly *via* an *N*-substituted intermediate." Repetition of the process gave a tetrapyrrane; the "reversal" of β-substituents thus involved rings A, B, and C rather than ring D. A final cyclisation, presumed to occur readily, then gave the macrocycle. In any such scheme involving intramolecular rearrangement, the reported isolation of formaldehyde [15] must be considered as the result of a side-reaction.

We have assumed that the polymerisation of porphobilinogen is a reaction involving carbonium ions and that it is an intramolecular process. The first assumption is at least

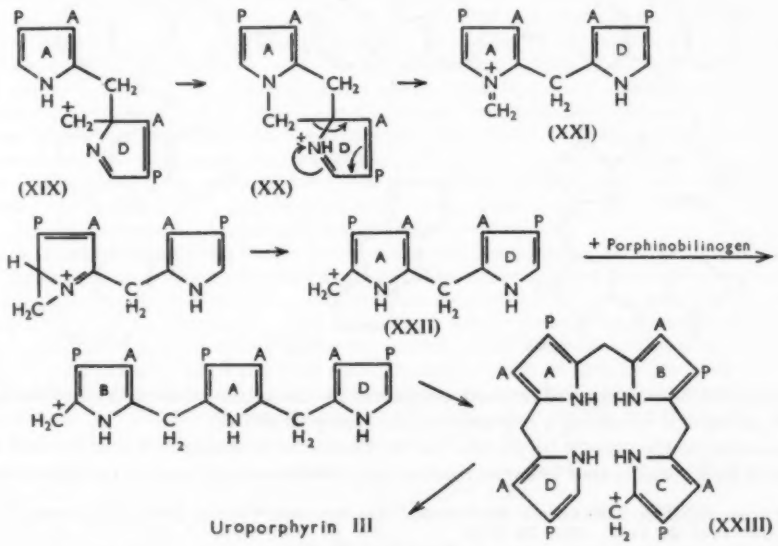
[19] Cookson and Rimington, *Biochem. J.*, 1954, **57**, 476.
[20] Rimington, *Ann. Reports*, 1954, **51**, 317.
[21] Jackson and MacDonald, *Canad. J. Chem.*, 1957, **35**, 715.
[22] Robinson, "Structural Relations of Natural Products," Oxford Univ. Press, 1955, p. 25.

partly justified by the fact that variation of pH seems to have little effect on the product, as judged by chromatographic analysis, and the second is supported by the preponderance



of III-type porphyrin in the product. The formation of I-type porphyrins is the consequence of an independent reaction involving the regular addition of porphobilinogen molecules involving attack by the carbonium ion at the 5- rather than the 2-position of the nucleus. The relative extent of these competing reactions is governed by electronic and steric factors; for example, it has been found that a blocking group such as ethoxycarbonyl in the 5-position has a very profound influence on the coupling reaction. The pyrroles (XV; R = OEt or hexamine salt) react with the α-free pyrrole (XVI) in dilute hydrochloric acid at 100° to give the mixed product (XVII) exclusively; the symmetrical dipyrromethane (XVIII) is formed only in the absence of (XVI).

For the conversion of porphobilinogen into uroporphyrin III we visualise an initial reaction similar to that already postulated by Cookson and Rimington [19] and by Robinson.[22] It is assumed that the intermediate (XIX) is formed from an attack of ring A on ring D, the subsequent stage being migration of the methylene group to the 5-position of ring A, rather than D. This migration involves the formation of a tricyclic intermediate and comprises the following stages:



The essential features of the present theory are: (i) reaction of the carbonium ion (XIX) at the nitrogen atom of ring A to form the tricyclic intermediate (XX); (ii) the fission of

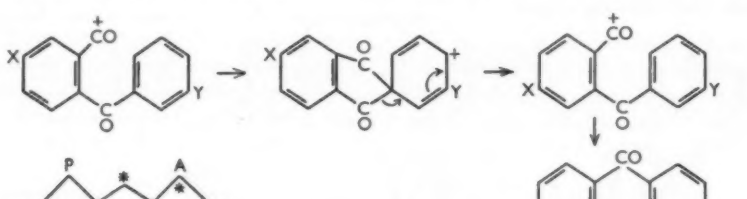
the new ring in the manner shown to yield the dipyrromethane (XXI); (iii) migration of the *N*-methylene substituent to the α-carbon as in (XXII), probably with the intermediate formation of a three-membered ring; (iv) repetition of the process (C ⟶ B ⟶ A ⟶ D) to give the tetrapyrrane (XXIII), and a final cyclisation and oxidation to uroporphyrin III. It will be observed that the methylene group originally attached to ring D migrates successively to rings A, B, and C and finally forms the link between rings C and D.

Whereas it is usual for electrophilic attack on the pyrrole nucleus to occur on carbon, it is nevertheless possible to obtain *N*-substitution, especially when the conditions are sterically favourable as in (XIX). The formation of the so-called pyrrocols (*e.g.*, XXIV) from pyrrole-α-carboxylic acids with acetic anhydride [23] is relevant in this connection, and the presence of alkyl substituents, known [17,24] to enhance the basic properties of the ring, favours *N*-substitution.

An attempt to obtain *N*-substituted pyrroles by direct condensation of either pyrrole itself [25] or kryptopyrrole with triphenylmethanol in glacial acetic acid was unsuccessful, only *C*-substitution being observed [strong infrared band at about 3450 cm.$^{-1}$ (NH)]. From a preparative point of view, the condensation of alkyl or acyl halides with *N*-potassiopyrroles in anhydrous media is the method of choice to achieve substitution on the nitrogen atom in the pyrrole series.

The mechanism suggested for the conversion of (XIX) into (XXI) is analogous to that proposed [26] for the Hayashi rearrangement of unsymmetrical benzoylbenzoic acids to anthraquinones,[27] and in both cases the juxtaposition of the reactive centres brings about the ready formation of the cyclic intermediate.

Migration of alkyl substituents from nitrogen to carbon is common in pyrrole chemistry but usually necessitates vigorous experimental conditions. However, it was expected that an *N*-methylenepyrrole cation (*e.g.*, XXI) would rearrange readily to the carbonium ion (XXII). In order to test this, *N*-methoxymethylopsopyrrole (XXV) was prepared from *N*-potassio-opsopyrrole and chloromethyl ether and it has been shown that the



(XXVI) (XXIV) (XXV)

product could be transformed into ætioporphyrin by the action of dilute hydrochloric acid at 100°, a reaction involving a migration of the type postulated.

According to the present suggestion for the biosynthesis of uroporphyrin, the first *meso*-bridge to be formed is that between rings A and D which corresponds to the direct linkage

[23] Fischer and Orth, "Die Chemie des Pyrroles," Leipzig, 1934, Vol. I, p. 236; Corwin *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 1151; 1956, **78**, 3135.
[24] Stedman and MacDonald, *Canad. J. Chem.*, 1955, **33**, 468.
[25] Khotinsky and Patzewitch, *Ber.*, 1909, **42**, 3104.
[26] Sandin, Melby, Crawford, and McGreer, *J. Amer. Chem. Soc.*, 1956, **78**, 3817.
[27] Hayashi *et al.*, *J.*, 1927, 2516; 1930, 1513, 1520, 1524; *Bull. Chem. Soc. Japan*, 1936, **11**, 184.

of two five-membered rings in vitamin B_{12}.[28] This suggests that the vitamin B_{12} macrocycle is formed from the appropriate porphyrinogen by fission and recyclisation, with a methylation step at some intermediate stage. In a preliminary communication [29] describing the structure of vitamin B_{12} it was pointed out that, if porphobilinogen could be converted into a tetracyclic, partially reduced intermediate such as (XXVI), there would be six positions (*) which would be susceptible to *C*-alkylation; and that these were the positions in which methyl groups occurred in the vitamin. We are at present using this biogenetic scheme as the basis of a synthesis of the vitamin B_{12} chromophore *in vitro* although it is no longer necessary to postulate an intermediate such as (XXVI).

Experimental

Ethyl 4-Acetyl-5-oxohexanoate.—Sodium (0·22 g.) was dissolved in absolute ethanol (200 c.c.) and acetylacetone (50 g.) was added, followed by ethyl acrylate (50 g.). The mixture was heated under reflux for 2 hr. on the water-bath, then kept overnight and neutralised with glacial acetic acid (0·33 g.). The ethanol was removed under reduced pressure. Distillation of the residue gave ethyl 4-acetyl-5-oxohexanoate, b. p. 146—150°/17 mm. (70 g., 70%) (Found: C, 59·7; H, 8·0. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·05%). March [30] gives b. p. 154—155°/15 mm.

Ethyl 3 : 4 : 5-Trimethylpyrrole-2-carboxylate (IX; R = Me).—(i) A solution of sodium nitrite (7·4 g.) in water (25 c.c.) was added to an ice-cooled, well-stirred solution of ethyl acetoacetate (13 g.) in glacial acetic acid (40 c.c.) at such a rate that the temperature remained <14°. After stirring of the cooled solution for a further 3 hr. it was kept overnight at room temperature and next day 3-methylpentane-2 : 4-dione [31] (11·4 g.) was added, followed by zinc dust (14 g.) at a rate which maintained the temperature of the mixture at 60°. The mixture was heated on the water-bath for 1 hr., poured into water, and then placed in the refrigerator for 2 hr. The suspended product was separated from excess of zinc by decantation and the pyrrole ester (7·5 g., 42%) removed by filtration and air-dried. After crystallisation from ethanol it formed colourless plates, m. p. 128° (lit.,[32] 128°) (Found: C, 66·1; H, 8·2; N, 8·0. Calc. for $C_{10}H_{15}O_2N$: C, 66·3; H, 8·35; N, 7·7%).

(ii) Pentyl nitrite (6·5 g.) was added to a stirred mixture of diethyl 3-oxoadipate [33] (10·8 g.) and concentrated hydrochloric acid (0·2 c.c.) at such a rate that the temperature remained <25°. After being kept overnight the product was added to a mixture of 3-methylpentane-2 : 4-dione (6·7 g.), glacial acetic acid (50 c.c.), ammonium acetate (8 g.), and zinc dust (2·5 g.) with vigorous stirring. A further quantity of zinc dust (5 g.) was added gradually while the temperature was kept at 60—65°. Then the product was heated on the water-bath for 2 hr., poured into water, and cooled in the refrigerator for several hr. The precipitated solid was separated and dissolved in hot ethanol (25 c.c.), and any remaining zinc separated by filtration. Water was added to the warm filtrate until a turbidity was produced and, after cooling, the pyrrole ester (2·25 g., 40%) was obtained as colourless plates, m. p. 128° (Found: C, 66·4; H, 8·3; N, 7·9%), identical with the product prepared as above.

Ethyl 4-2′-Ethoxycarbonylethyl-3 : 5-dimethylpyrrole-2-carboxylate (IV; R = H, R′ = Et).—(i) Ethyl acetoacetate (13 g.) was nitrosated in the manner described in the first preparation of ethyl 3 : 4 : 5-trimethylpyrrole-2-carboxylate (above) and, the following day, ethyl 4-acetyl-5-oxohexanoate (20 g.) was added. Zinc dust (14 g.) was introduced into the stirred mixture at such a rate that the temperature was maintained at 65°. After the addition of the zinc, the product was heated on the water-bath for 1 hr., then poured on crushed ice. The suspension of the *product* was decanted from any excess of zinc, then separated by filtration and crystallised from ethanol: it formed colourless needles (11·7 g., 44%), m. p. 73° (lit.,[34] 73°) (Found: C, 62·9; H, 7·6; N, 5·2. Calc. for $C_{14}H_{21}O_4N$: C, 63·1; H, 7·85; N, 5·2%).

[28] Hodgkin, Pickworth, Robertson, Trueblood, Prosen, and White, *Nature*, 1955, **176**, 325; Bonnett, Cannon, Clark, Johnson, Parker, Smith, and Todd, *J.*, 1957, 1158.
[29] Bonnett, Cannon, Johnson, Sutherland, Todd, and Smith, *Nature*, 1955, **176**, 328.
[30] March, *Ann. Chim.* (*France*), 1902, **26**, 333.
[31] von Auwers and Jacobsen, *Annalen*, 1921, **426**, 227.
[32] Fischer and Walach, *ibid.*, 1926, **450**, 109.
[33] MacDonald and Stedman, *Canad. J. Chem.*, 1955, **33**, 458.
[34] Fischer and Süs, *Annalen*, 1930, **484**, 113.

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(ii) Sodium nitrite (3·7 g.) in water (12·5 c.c.) was added dropwise with stirring and cooling to diethyl 3-oxoglutarate [35] (10·1 g.) in glacial acetic acid (20 c.c.) at <14°. Stirring was continued for a further 3 hr. and the mixture kept overnight at room temperature. After the addition of ethyl 4-acetyl-5-oxohexanoate (10 g.), zinc dust (7 g.) was added to the stirred mixture at 65°. Stirring was continued for another 30 min. and the product then heated on the water-bath for 1 hr., cooled, and poured on crushed ice. The precipitated oil slowly solidified at 0°. It crystallised from ethanol as colourless plates of the pyrrole ester (2·2 g., 16·5%), m. p. 73° after several crystallisations from ethanol (Found: C, 62·9; H, 7·5; N, 5·2%).

Benzyl 4-2′-Ethoxycarbonylethyl-3 : 5-dimethylpyrrole-2-carboxylate (IV; R = H, R′ = CH_2Ph).—Sodium nitrite (21·6 g.) in water (50 c.c.) was added with stirring to benzyl acetoacetate (50 g.) in glacial acetic acid (80 c.c.) at <10°. The cooled mixture was stirred for a further 4 hr., then kept overnight at room temperature and added to ethyl 4-acetyl-5-oxohexanoate (56·5 g.) in acetic acid (100 c.c.) in the presence of zinc dust (34 g.) with stirring, at about 70°. The mixture was heated under reflux for 30 min., then poured on crushed ice (*ca.* 1 kg.). The *ester* was separated, washed with water, and crystallised twice from aqueous ethanol, forming colourless needles (30 g., 35%), m. p. 75—76° (Found: C, 69·0; H, 6·85; N, 4·2. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·05; N, 4·25%).

Benzyl 5-Acetoxymethyl-4-2′-ethoxycarbonylethyl-3-methylpyrrole-2-carboxylate (IV; R = OAc, R′ = CH_2Ph).—To benzyl 4-2′-ethoxycarbonylethyl-3 : 5-dimethylpyrrole-2-carboxylate (IV; R = H, R′ = CH_2Ph) (7 g.) in glacial acetic acid (600 c.c.), lead tetra-acetate (9·4 g.) was added with stirring during 30 min. Stirring was continued for a further 3 hr., after which most of the solvent was removed under reduced pressure. The residue was poured into ice-cold water (*ca.* 800 c.c.) and kept overnight. The colourless precipitate was separated, washed with water, and crystallised from acetone as colourless needles (5·5 g., 67%), m. p. 121—122° (Found: C, 65·0; H, 6·8; N, 4·0. $C_{21}H_{25}O_6N$ requires C, 65·1; H, 6·5; N, 3·6%).

Coproporphyrin III Tetraethyl Ester (II; R = Me, P = $CH_2{\cdot}CH_2{\cdot}CO_2Et$).—The above acetoxy-compound (IV; R = OAc, R′ = CH_2Ph; 2·5 g.) in ether (150 c.c.) was shaken with a little Raney nickel to remove any catalyst poisons. The nickel was separated and the filtrate hydrogenated in the presence of 5% palladium–charcoal (0·2 g.) and triethylamine (3 drops). Hydrogenolysis of the benzyl group was complete after about 6 hr., then the catalyst was separated and the solvent removed at room temperature and reduced pressure. The resulting pyrrole acid darkened very rapidly in air and could not be purified completely.

The residue after removal of the ether was heated in ethanol (40 c.c.) and glacial acetic acid (10 c.c.) on the water-bath for 90 min. The colour changed from brown to deep red and the resulting solution was then aerated for *ca.* 10 hr. Chloroform (100 c.c.) was next added and the solution washed with aqueous sodium carbonate, then water, and dried (Na_2SO_4). The solution was concentrated to 20 c.c. and chromatographed on an alumina column (Spence type H; 30 × 1·5 cm.). Elution of the product was followed by means of a hand spectroscope. Removal of the solvent from the main porphyrin fraction gave coproporphyrin III tetraethyl ester (185 mg., 15% based on the pyrrole benzyl ester) which crystallised from chloroform–methanol in thin reddish-brown needles, m. p. 147—149° (micro hot-stage) (lit.,[10] 124°, not sharp) (Found: C, 68·8; H, 6·95; N, 7·05. Calc. for $C_{44}H_{54}O_8N_4$: C, 68·9; H, 7·1; N, 7·3%), $\lambda_{max.}$ in $CHCl_3$: 400, 499, 534, 569, and 620 mμ (log ε 5·22, 4·12, 3·95, 3·76, and 3·60 respectively).

tert.-*Butyl 3 : 4 : 5-Trimethylpyrrole-2-carboxylate*.—Redistilled *tert.*-butyl acetoacetate (31·6 g.) in glacial acetic acid (80 c.c.) was treated with aqueous sodium nitrite (14·8 g. in 50 c.c). with stirring during 20 min., at 10—12° (ice-cooling). The product was kept for a further 2 hr. at 4°, then overnight at room temperature. The following day, 3-methylpentane-2 : 4-dione (22·8 g.) was added with stirring, followed by zinc dust (28 g.) at such a rate as to keep the reaction temperature at 80—85°. Next, the mixture was stirred for a further 30 min., then heated to 100° for 2 hr. The hot solution was poured, with stirring, into cold water (1 l.), and the precipitated solid separated and dissolved in hot ethanol (500 c.c.). The clarified solution was diluted with water to produce a faint turbidity and then kept, the *ester* being obtained as colourless needles (13 g.), m. p. 137—138° (Found: C, 69·0; H, 8·85; N, 6·7. $C_{12}H_{19}O_2N$ requires C, 68·85; H, 9·15; N, 6·7%).

tert.-*Butyl 5-Acetoxymethyl-3 : 4-dimethylpyrrole-2-carboxylate*.—The foregoing ester (5 g.) in glacial acetic acid (150 c.c.) was treated with lead tetra-acetate (10·6 g.) in ½ hr. at room temperature with stirring. After a further 2 hours' stirring, most (80 c.c.) of the acetic acid

[35] MacDonald and MacDonald, *Canad. J. Chem.*, 1955, **33**, 573.

was removed on the water-bath under reduced pressure and the residue poured into water (1 l.) with stirring. The colourless precipitate was separated, washed, dried (5·85 g.), and crystallised from aqueous acetone, forming colourless needles, m. p. 127—128° (Found: C, 63·3; H, 7·95; N, 5·0. $C_{14}H_{21}O_4N$ requires C, 62·9; H, 7·9; N, 5·25%).

Octamethylporphin.—tert.-Butyl 5-acetoxymethyl-3 : 4-dimethylpyrrole-2-carboxylate (1 g.) was suspended in ethylene glycol (10 c.c.) and heated under reflux for 75 min. The dark solution was cooled, diluted with methanol (40 c.c.), and aerated for 10 hr., further methanol being added when necessary to maintain the volume. The very dark precipitated solid (0·13 g.) was separated and extracted with methanol, and the insoluble residue continuously extracted from a thimble with chloroform (10 c.c.). From the extract there was obtained octamethylporphin (87 mg., 22%), $\lambda_{max.}$ in *o*-dichlorobenzene at 404, 501, 535, 573, and 603 mμ (log ε 5·11, 4·10, 3·93, 3·76, and 3·68 respectively).

Ethyl 5-Acetoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate.—Lead tetra-acetate (17·1 g.) was added gradually, during ½ hr., to a solution of ethyl 4-ethyl-3 : 5-dimethylpyrrole-2-carboxylate (5 g.) in glacial acetic acid (150 c.c.) at room temperature. The solution was stirred for a further 3 hr., then poured into water (500 c.c.). The precipitated white solid was separated, washed, and dried (4·4 g., 68%). After crystallisation from aqueous acetone it formed colourless needles, m. p. 128°, unchanged on being heated in acetic anhydride (Found: C, 61·6; H, 7·6; N, 5·5. $C_{13}H_{19}O_4N$ requires C, 61·65; H, 7·55; N, 5·5%).

Ethyl 5-Ethoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate.—The above acetoxymethyl compound (4·4 g.) was heated in ethanol (50 c.c.) under reflux for 30 min. The solution was cooled and the *product* crystallised as colourless needles (3·0 g., 72%), m. p. 56—58° (Found, on a sample sublimed at 50°/0·1 mm.: C, 64·8; H, 8·85; N, 5·8. $C_{13}H_{21}O_3N$ requires C, 65·2; H, 8·85; N, 5·85%).

Ethyl 4-Ethyl-3-methyl-5-(N-methyleneaminomethyl)pyrrole-2-carboxylate (XV; R = N:CH_2). —Ethyl 5-chloromethyl-4-ethyl-3-methylpyrrole-2-carboxylate [7] (0·5 g.) and hexamine (0·33 g.) were heated in chloroform (15 c.c.) under reflux for 1 hr. The solution was cooled, acetone (15 c.c.) was added, and the white crystalline salt (0·7 g.) so obtained was separated and washed with acetone. It was then dissolved in water (15 c.c.) and heated on the steam-bath, the solution rapidly becoming cloudy, and after 1 hr. a yellow gummy solid separated. The precipitated solid was dissolved in warm aqueous ethanol and, after cooling, a white crystalline *compound* (0·2 g.) was obtained which was insoluble in water but soluble in 3N-hydrochloric acid. It recrystallised from ethyl acetate–acetone as plates, m. p. 145—147° (Found: C, 64·45; H, 8·2; N, 12·8. $C_{12}H_{18}O_2N_2$ requires C, 64·85; H, 8·15; N, 12·6%).

The same product was obtained by a similar method from ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate.[36]

Diethyl 3 : 3'-Diethyl-4 : 4'-dimethyldipyrromethane-5 : 5'-dicarboxylate (XVIII) (i).—Ethyl 5-ethoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate (2 g.) was heated in ethanol (30 c.c.) containing hydrochloric acid (5 c.c. of concentrated) under reflux for 30 min. After cooling, the crystalline solid (1·3 g., 83%) was separated, washed, dried, and crystallised from ethanol, forming colourless needles, m. p. 126° (lit.,[37] 126°). The formaldehyde also formed in the reaction was identified by bubbling the gaseous products from the reaction in a stream of nitrogen through a solution of 2 : 4-dinitrophenylhydrazine. The derivative (corresponding to 0·75 mol.) had m. p. and mixed m. p. 165—167°.

(ii) The hexamine salt from ethyl 5-chloromethyl-4-ethyl-3-methylpyrrole-2-carboxylate (2 g.; preparation as above) was dissolved in ethanol (10 c.c.) and water (10 c.c.); 10N-hydrochloric acid (5 c.c.) was added and the mixture heated under reflux for 4 hr. On cooling, colourless needles (0·65 g.) were obtained which had m. p. 119°, raised to 126° on crystallisation from ethanol. The m. p. was undepressed on admixture with the product of the previous experiment.

Diethyl 3-Ethyl-4 : 3' : 4'-trimethyldipyrromethane-5 : 5'-dicarboxylate (XVII).—(i) A mixture of ethyl 5-ethoxymethyl-4-ethyl-3-methylpyrrole-2-carboxylate (256 mg.) and ethyl 3 : 4-dimethylpyrrole-2-carboxylate (251 mg.; prepared by decarboxylation [38] of 5-ethoxycarbonyl-3 : 4-dimethylpyrrole-2-carboxylic acid [39]) was dissolved in ethanol (100 c.c.), concentrated

[36] Fischer and Ernst, *Annalen*, 1926, **447**, 139.
[37] Fischer and Halbig, *ibid.*, p. 123.
[38] Fischer and Höfelmann, *ibid.*, 1938, **533**, 216.
[39] Fischer and Hierneis, *ibid.*, 1931, **492**, 21.

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sulphuric acid (2 c.c.) was added, and the mixture heated under reflux for 4 hr. After storage for 2 weeks a quantity of a colourless solid had crystallised from the dark red solution. This was separated and after crystallisation from light petroleum (b. p. 60—80°) formed colourless needles, m. p. 174—176°. A further quantity was obtained by dilution of the mother-liquors and after crystallisation from ethanol had m. p. 173—174° (Found: C, 66·6; H, 7·4; N, 8·1. $C_{20}H_{26}O_4N_2$ requires C, 66·6; H, 7·7; N, 7·7%).

(ii) The hexamine salt (370 mg.) from ethyl 5-bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate and ethyl 3 : 4-dimethylpyrrole-2-carboxylate were dissolved in ethanol (20 c.c.) and treated with concentrated hydrochloric acid (2 c.c.) in water (20 c.c.). The mixture was heated on the water-bath for 4 hr. although a precipitate was obtained after *ca.* 10 min. The resulting suspension was cooled and the solid product (295 mg.) separated, washed with aqueous ethanol, and dried; it had m. p. 173°, raised to 175° on crystallisation from aqueous ethanol. The m. p. was unchanged on admixture with the product from the previous experiment (Found: C, 66·9; H, 7·7; N, 7·9%).

3-Ethyl-1-methoxymethyl-4-methylpyrrole; *1-Methoxymethylopsopyrrole* (XXV).—Freshly distilled opsopyrrole (3·3 g.; prepared by an adaptation of the method given by Eisner, Linstead, Parkes, and Stephen [40] for 3 : 4-dimethylpyrrole) was dissolved in light petroleum (b. p. 100—120°; 25 c.c.) and treated with potassium (1 g.) in small pieces. The mixture was heated under reflux for 12 hr., until all the metal had dissolved. Then the colourless potassium salt was separated, washed with dry ether, suspended in dry ether (150 c.c.), and treated with chloromethyl ether (13·2 g.; freshly distilled) in dry ether (40 c.c.) which caused the solvent to reflux. Next the product was heated under reflux on the water-bath for 15 min. and the solid material separated. Removal of the solvent under reduced pressure from the filtrate gave a yellow oil which rapidly darkened in contact with air. Attempted distillation under reduced pressure caused the formation of an intractable red gum. The yellow oil was therefore used in the following experiment without further purification.

Ætioporphyrin.—1-Methoxymethylopsopyrrole (1 g.) from the foregoing experiment was dissolved in ethanol (5 c.c.), treated with 2N-hydrochloric acid (3 c.c.), and heated under reflux for 1 hr. The resulting solution was aerated for 4 hr. and the red resinous precipitate separated and dissolved in a small volume of chloroform (3 c.c.). Addition of methanol (6 c.c.) caused precipitation of a dark red solid (0·25 g.) which was very soluble in chloroform to give a solution which showed the typical porphyrin spectrum (log $\varepsilon_{max.}$ 4·88 at 398 mμ, *i.e.*, approx. 50% pure). Purification was achieved by chromatography of the chloroform solution on alumina (15 × 1 cm.) and elution with chloroform: the porphyrin fraction was easily separated. Removal of the solvent gave ætioporphyrin (120 mg.) which was further purified by crystallisation from chloroform–methanol (1 : 2) and sublimation at 210°/0·1 mm. Its light absorption in $CHCl_3$ had max. at 398, 498, 533, 567, and 620 mμ (log ε 5·17, 4·05, 3·92, 3·75, and 3·57 respectively).

2-Triphenylmethylpyrrole.—Prepared according to Khotinsky and Patzewitch,[25] it had m. p. 252° after crystallisation from ethanol. The infrared spectrum showed a strong band at 3460 cm.$^{-1}$.

4-Ethyl-3 : 5-dimethyl-2-triphenylmethylpyrrole.—Kryptopyrrole (130 mg.) and triphenylmethanol (250 mg.) were heated with glacial acetic acid (1·5 c.c.) in a sealed tube at 100° for 2 hr. After cooling, the yellow crystalline product (200 mg.) was separated and washed with ether. After crystallisation from ethanol it had m. p. 156—158° (Found: C, 88·5; H, 7·55; N, 3·7. $C_{27}H_{27}N$ requires C, 88·7; H, 7·45; N, 3·8%). The infrared spectrum showed a strong band at 3446 cm.$^{-1}$.

Grateful acknowledgment is made to the Department of Scientific and Industrial Research for the award of Maintenance Grants (to E. B., E. M., and K. B. S.) and to several colleagues, especially Professor Melvin S. Newman, for helpful and stimulating discussions. We thank Professor C. Rimington, F.R.S., Professor A. Neuberger, F.R.S., Imperial Chemical Industries Limited (Paints and Dyestuffs Divisions), and British Industrial Solvents Ltd., for generous gifts of chemicals.

UNIVERSITY OF NOTTINGHAM. [*Received, November 12th*, 1957.]

[40] Eisner, Linstead, Parkes, and Stephen, *J.*, 1956, 1655.

288 cis- *and* trans-2 : 3-*Dichlorohexafluorobut*-2-*ene.*

By (Mrs.) F. Dickinson, R. Hill, and J. Muray.

2 : 3-Dichlorohexafluorobut-2-ene has been prepared by dechlorination of 2 : 2 : 3 : 3-tetrachlorohexafluorobutane by means of zinc. The *cis*- and the *trans*-isomer were separated by gas–liquid chromatography, and the stereoisomers identified on the basis of chemical analyses, molecular-weight determinations, and mass-spectrometric, nuclear magnetic resonance, and infrared spectroscopic examinations of the materials.

Some physical properties of the two isomers are given.

Henne and his co-workers described the preparation of 2 : 3-dichlorohexafluorobut-2-ene from octachlorobut-2-ene and a mixture of antimony trifluoride and antimony dichlorotrifluoride [1,2] and by the dehydrochlorination of 2 : 3 : 3-trichloro-1 : 1 : 1 : 4 : 4 : 4-hexafluorobutane.[3] The structure of the products, mixtures of *cis*- and *trans*-2 : 3-dichlorohexafluorobut-2-ene, was confirmed by quantitative oxidation to trifluoroacetic acid.

We now describe the preparation, separation, and identification of the stereoisomers. Gas–liquid chromatography was applied on a preparative scale in their separation and mass-spectrometry and infrared and nuclear magnetic resonance spectroscopy in their identification. Dechlorination of 2 : 2 : 3 : 3-tetrachlorohexafluorobutane was chosen because it could yield only the desired compound.

Table 1. *Physical properties of the isomers.*

	Isomer I (*trans*)	Isomer II (*cis*)		Isomer I (*trans*)	Isomer II (*cis*)
B. p.	66·2°	67·9°	V. p. (mm. Hg) at 25° ...	157	146
F. p.	−53	−108	,, ,, 50°	429	403
n_D^{20}	1·3477	1·3471	,, ,, 65° ...	731	689

The results obtained in the measurements of vapour pressures (in mm.) in the temperature range 15—70° fitted the equations:

Isomer I (*trans*) $\log p = 7{\cdot}8432 - 1684/T$; isomer II (*cis*) $\log p = 7{\cdot}8621 - 1699/T$ where T is given in °K.

Preparation, Separation, and Physical Properties of the Isomers.—The isomers could not be separated by fractional distillation through a 15-plate column. Gas–liquid chromatography showed that various cuts of the 2 : 3-dichlorohexafluorobut-2-ene fraction consisted of two different entities in proportions varying from cut to cut. Subsequently, these components were proved to be *trans*- and *cis*-2 : 3-dichlorohexafluorobut-2-ene.

The isomers were, however, separated by gas–liquid chromatography on a preparative scale. Although separation was better at low temperatures, the retention times were too high to make this practicable on a larger scale and working at 85° was considered advantageous.

Chemical analyses and molecular weights of the isomers were in good agreement with theory; some physical properties are given in Table I.

Identification of the Stereoisomers.—The mass-spectrometric results (Table 2) showed that the two materials had similar but not identical cracking patterns. Since the possibility of ion-rearrangements could not be ruled out, the similarity of the patterns was not sufficient evidence to show that the two materials were stereoisomers.

Only a single ^{19}F peak, but at different field strength in each case, was obtained in the nuclear magnetic resonance spectra. The single peaks indicated that all the fluorine atoms were at equivalent sites in the molecules; there must therefore be two CF_3 groups in the molecule of each. This suggestion was confirmed by the absence of any multiplet fine-structure of the ^{19}F peaks. A fine structure would have appeared had the fluorine atoms

[1] Henne and Trott, *J. Amer. Chem. Soc.*, 1947, **69**, 1820.
[2] Henne and Newby, *ibid.*, 1948, **70**, 130.
[3] Henne *et al.*, *ibid.*, 1945, **67**, 1906.

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been attached to adjacent carbon atoms. The structure of both compounds must accordingly be $CF_3 \cdot CCl{:}CCl \cdot CF_3$.

The evidence needed for identifying the isomers was provided by infrared spectroscopy. The results show C=C absorption at 6·2 μ in isomer II but not in isomer I. The absence of this absorption shows isomer I to have the symmetrical *trans*-configuration, where no

TABLE 2. *Some ion peaks of the mass spectra of the isomers.*

Mass No.		Relative intensity of peak Isomer I (*trans*)	Isomer II (*cis*)	Mass No.		Relative intensity of peak Isomer I (*trans*)	Isomer II (*cis*)
232	$C_4Cl_2F_6$	81	73	132	$C_2Cl_2F_2$	0·4	0·3
213	$C_4Cl_2F_5$	16	21	93	C_2F_3	31	26
197	C_4ClF_6	27	26	85	$CClF_2$	8	8
182	$C_3Cl_2F_4$	4	3	69	CF_3	79	76
163	$C_3Cl_2F_3$	100	100	66	CClF	0·9	0·8
147	C_3ClF_4	36	33	50	CF_2	1	1
143	C_4F_5	4	4	47	CCl	2	2

change in dipole moment would be associated with the C=C stretching vibration. Examination of models shows that the *cis*-configuration would be strained at this bond and a change of dipole moment would accompany the C=C stretching vibration, resulting in infrared absorption.

It is therefore concluded that isomer I is *trans*-, and isomer II *cis*-2 : 3-dichlorohexafluorobut-2-ene.

EXPERIMENTAL

Dechlorination of 2 : 2 : 3 : 3-*Tetrachlorohexafluorobutane*.—The chlorofluorocarbon was added dropwise to the stirred mixture of zinc dust (about 400 g.), *n*-butyl alcohol (1·2 l.), and glacial acetic acid (5 ml.), at 85—95°; in no run were more than 2 g. of the chlorofluorocarbon used per g. of zinc dust. The product passed through a fractionating column kept at 55° and was collected in traps at 0° and −80°.

Purification.—The product (obtained in 88% yield) was refluxed for 1½ hr. over phosphoric oxide, cooled, filtered, and fractionally distilled in a still of 15 theoretical plates efficiency at the rate of 10—15 g. of distillate per hr. The fractions were examined by gas-phase chromatography, a Griffin Mark I V.P.C. unit being used with di-(3 : 5 : 5-trimethylhexyl) phthalate on kieselguhr (" Celite ") as stationary phase, and their refractive indices and molecular weights determined.

Of the product (418 g.) which had been refluxed with phosphoric oxide, 3·5% distilled at 32—34°, 12·5% at 34—67°, 70% at 67—68·5°, and 5% at 69°, the rest being hold-up and residues. The main fraction, b. p. 67—68·5°, which was a mixture of *trans*- and *cis*-2 : 3-dichlorohexafluorobut-2-ene, had n 1·347, M 234·4 ± 0·5.

Separation of Stereoisomers.—A column, 16 ft. long, 1·46 in. diam., packed with " Celite " 545 (1990 g.), graded [4] by elutriation with water and impregnated with dibutyl phthalate (853 g.) was used. About 8 g. of the mixture of isomers were injected into the column at 85°, the inlet and outlet pressures being respectively 840 and 755 mm., through which nitrogen was passed at the rate of 20 l./hr. measured at 20° at 760 mm. A thermal conductivity cell was used for detection, and the fractions were collected in liquid-air traps. From 16 runs, 28 g. of pure *trans*-, 43 g. of practically pure *cis*-, and 24 g. of a mixture of the two isomers were isolated. Part of the *cis*-sample was recycled, giving 19 g. of pure material. The maximum of the peak for the *trans*-isomer appeared after 54·5 min. from the time of injection, and that of the *cis*- after 65·5 min. The corresponding time for argon was 11·8 min. The separated materials were examined by gas–liquid chromatography, a number of stationary liquid phases being used including dinonyl phthalate, polyethylene glycol 400, and silicone oil MS 550. No band due to impurity was detected by these materials. (Found, for the *trans*-isomer: C, 21·1; Cl, 30·7; F, 48·7%; M, 233·5 ± 0·5. For the *cis*-isomer: C, 21·2; Cl, 30·5; F, 48·5%; M, 234·0 ± 0·5. Calc. for $C_4Cl_2F_6$: C, 20·6; Cl, 30·5; F, 48·9%; M, 233.)

[4] James and Martin, *Biochem. J.*, 1952, **50**, 679.

Determination of Properties and Identification of Isomers.—The vapour pressures were measured in the temperature range 15—70° with a static isoteniscope by using a standard procedure,[5] and the freezing points on 2 ml. samples with a calibrated thermocouple.

The authors thank their colleagues Dr. D. G. Stevenson for mass-spectrometric and infrared spectral examinations; Mr. J. Adams for the determination of some of the physical properties; Mr. J. Parle and Miss B. Murray for assistance in the experimental work; Mr. F. P. Johnson for analyses; and Mr. A. N. Hamer, of U.K.A.E.A., Capenhurst, for nuclear magnetic resonance examinations.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, GENERAL CHEMICALS DIVISION,
RESEARCH DEPARTMENT, WIDNES LABORATORY,
WIDNES, LANCS. [*Received, November 13th*, 1957.]

[5] Smith and Menzies, *J. Amer. Chem. Soc.*, 1910, **32**, 1412.

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289. *Trypanocides of the Phenanthridine Series. Part II.* Pyrimidinyl-phenanthridines.*

By T. I. WATKINS.

Phenanthridinium compounds, some of which exhibit a highly curative action in bovine trypanosomiasis, and 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide gave pyrimidinyl-phenanthridines, some of which are potent trypanophylactics.

MANY phenanthridinium compounds prepared by Morgan and Walls [1] and Watkins [2] are effective against *Trypanosoma congolense* infections of mice and *T. congolense* and *T. vivax* infections of cattle. However, the period of protection from infection conferred [3–5] by these compounds is short compared with that claimed for "Antrycide Pro-salt" (I; X = Cl and $MeSO_4$).[6,7]

The high prophylactic activity shown by "Antrycide" may be due, in part, to the presence of the pyrimidinium moiety. Compounds were therefore prepared in which this moiety had been introduced into the more active phenanthridinium salts. Some of these, prepared from a phenanthridinium salt and 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (II), were highly prophylactic in *T. congolense* infections of mice [8] and in *T. congolense* and *T. vivax* infections of cattle.[9] It was surprising that these compounds are also highly efficient curative agents in *T. congolense* infections of mice since the efficiency of the phenanthridinium compounds in this respect is markedly reduced by substitution of the free amino-groups.[10–13]

Compounds, of four main types, (III), (IV), (V), and (VI), were synthesised, all from the pyrimidinium iodide (II): compounds (III) from the 7-amino-grouping of a phenanthridinium compound, structures (IV) from 2 : 7-diaminophenanthridinium salts, structures (V) from a 3-aminophenanthridinium compound (VIII), and compound (VI) from the appropriate 9-*p*-aminophenylphenanthridinium salt. In structure (V) the

* Part I, *J.*, 1952, 3059.

[1] Morgan and Walls, *J.*, 1938, 389, and subsequent papers.
[2] Watkins, *J.*, 1952, 3059.
[3] Goodwin and Chandler, *Brit. J. Pharmacol.*, 1952, **7**, 591.
[4] Karib and Meal, *ibid.*, 1954, **9**, 37.
[5] Leach, Karib, Ford, and Wilmshurst, *J. comp. Path.*, 1955, **65**, [2], 130.
[6] Curd and Davey, *Brit. J. Pharmacol.*, 1950, **5**, 25.
[7] Davey, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1950, **43**, 583 *et seq.*
[8] Woolfe, in the press.
[9] Watkins and Woolfe, *Nature*, 1956, **178**, 368.
[10] Walls *et al.*, *J.*, 1945, 294.
[11] *Idem, ibid.*, 1946, 1031.
[12] *Idem, ibid.*, 1947, 67.
[13] Woolfe, *Brit. J. Pharmacol.*, 1956, **11**, 334.

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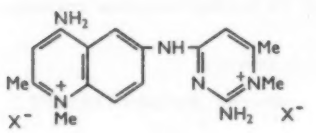
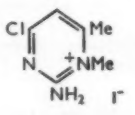
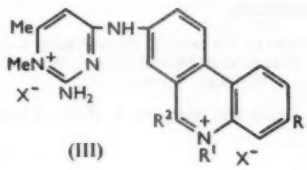
skeleton of the "Antrycide" molecule has been retained, and compound (VI) was of interest in that all the features essential for maximal activity in a phenanthridinium compound [10,12] were present. Compounds (III) and (V) were prepared in hot aqueous solution, in the presence of one equivalent of hydrochloric acid, which facilitated dissolution of the phenanthridinium compound and in one preparation had catalytic effect (cf. preparation of "Antrycide" and its derivatives [14]). When both 2- and 7-amino-groupings of the



(I)



(II)



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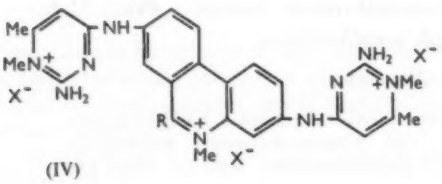
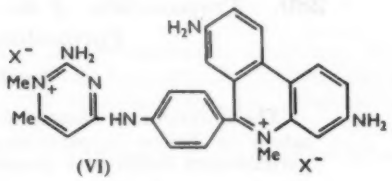
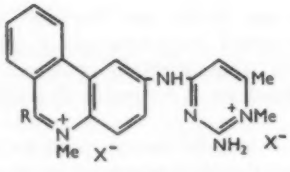


(IV)



(VI)



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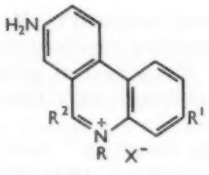
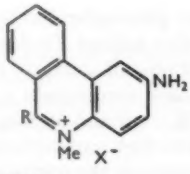


(VII)



(VIII)

phenanthridinium compound were available for reaction [*e.g.* preparation of compounds (III; R = NH_2)] preferential substitution occurred at the 7-amino-position (see also the monoacetylation [15] of 2 : 7-diaminophenanthridinium compounds). Walls suggests [10] that the dark-red colour of the 2 : 7-diaminophenanthridinium compounds is due to a benzenoid–quinonoid resonance in which the positive charge of the quaternary nitrogen atom is shared by the 2-amino-group, thus reducing the electronegative character of the latter. Proof that the major product from the condensation of the iodide (II), with 2 : 7-diamino-10-methyl-9-phenylphenanthridinium bromide (VII; R = Me, R′ = NH_2, R^2 = Ph, X = Br) was a 2-amino-7-(2-amino-6-methyl-4-pyrimidinylamino)-9-phenylphenanthridine 10 : 1′-dimetho-salt (III; R = NH_2, R^1 = Me, R^2 = Ph) was obtained by its unequivocal synthesis from 7-amino-10-methyl-2-nitro-9-phenylphenanthridinium chloride (VII; R = Me, R^1 = NO_2, R^2 = Ph, X = Cl) [16] and the pyrimidinium iodide (II), followed by reduction.

Compounds (IV) could not be prepared pure in aqueous solution or in aqueous solution in the presence of one or two equivalents of hydrochloric acid. The condensation proceeded smoothly, however, in phenol.

Experimental

Unless otherwise stated, compounds were dried for 2 hr. at 100°/2 mm. before analysis, since when compounds had been crystallised from an alcohol the solvent could not always be

[11] Barrett, Curd, and Hepworth, *J.*, 1953, 50.
[15] B.P. 746,027.
[16] Walls, *J.*, 1950, 3511.

completely removed at 100° under normal pressure. Pyrimidinylphenanthridinium chlorides quickly absorbed atmospheric moisture.

All analyses for water were carried out in a Karl Fischer apparatus modified to semimicro-scale.

*Preparation of Phenanthridinium Compounds.**

2 : 7-*Dinitrophenanthridines.*—*p*-Toluoyl chloride (14·2 ml.) and 2-amino-4 : 4′-dinitrodiphenyl [18] (25·9 g.) were heated in refluxing chlorobenzene (125 ml.) for 1 hr. to give 4 : 4′-*dinitro*-2-p-*toluamidodiphenyl* (35 g.), prisms, (from acetic acid), m. p. 203° (Found: N, 11·2. $C_{20}H_{15}O_5N_3$ requires N, 11·1%). The amide (30 g.), phosphorus oxychloride (10 ml.), and nitrobenzene (170 ml.) were heated under reflux for 2½ hr. Unchanged phosphorus oxychloride and some nitrobenzene were removed by distillation and ethanol (100 ml.) was then added at 80—100°. The *phenanthridine* (25 g.) which separated formed cream-coloured elongated plates (from acetic acid), m. p. 271—272° (Found: N, 11·9. $C_{20}H_{13}O_4N_3$ requires N, 11·7%).

2-p-iso*Propylbenzamido-* (94%), prisms (from acetic acid), m. p. 196—197° (Found: N, 10·3. $C_{22}H_{19}O_5N_3$ requires N, 10·35%), 2-p-*chlorobenzamido-* (94%), plates (from acetic acid), m. p. 211—212° (Found: N, 10·8. $C_{19}H_{12}O_5N_3Cl$ requires N, 10·55%), and 2-*anisoylamino*-4 : 4′-*dinitrodiphenyl* (91%), needles (from acetic acid), m. p. 211—212° (Found: N, 10·5. $C_{20}H_{15}O_6N_3$ requires N, 10·7%), were similarly prepared and cyclised to the following 2 : 7-*dinitrophenanthridines*: 9-p-iso*propylphenyl-* (86%), plates (from 2-ethoxyethanol), m. p. 275—276° (Found: N, 10·7. $C_{22}H_{17}O_4N_3$ requires N, 10·85%); 9-p-*chlorophenyl-* (89%), yellow plates (from 2-ethoxyethanol), m. p. 317—319° (Found: C, 60·3; H, 2·65; N, 11·4. $C_{19}H_{10}O_4N_3Cl$ requires C, 60·0; H, 2·6; N, 11·05%); and 9-p-*methoxyphenyl-* (83%), yellow needles (from 2-ethoxyethanol), m. p. 263—264° (Found: N, 11·0. $C_{20}H_{13}O_5N_3$ requires N, 11·2%).

2 : 7-*Diamino*-10-*methylphenanthridinium Bromides* (as VII; R = Me, $R^1 = NH_2$, X = Br).—2 : 7-Dinitro-9-*p*-tolylphenanthridine (7·5 g.) and methyl sulphate (4 ml.) were heated in nitrobenzene (50 ml.) for 1 hr. at 180°. After removal of nitrobenzene addition of hydrobromic acid solution (48%; 5 ml.) gave the quaternary bromide which was reduced by iron powder (9 g.) for 4 hr. in boiling ethanol (150 ml.), water (300 ml.), and 5N-hydrobromic acid (0·5 ml.). The mixture was filtered and the pH of the filtrate raised to 8·5 with ammonia solution. This mixture was set aside overnight and then filtered through kieselguhr. The filtrate was concentrated to about 50 ml., and the deposit crystallised from ethanol yielding dark-red plates of 2 : 7-*diamino*-10-*methyl*-9-p-*tolylphenanthridinium bromide* (3·8 g.), m. p. 270—271° (decomp.) (Found: N, 10·4; Br, 20·6. $C_{21}H_{20}N_3Br$ requires N, 10·65; Br, 20·3%).

The following 2 : 7-*diamino*-10-*methylphenanthridinium bromides* were similarly prepared from the dinitrophenanthridines described above: 9-p-iso*propylphenyl-* (41·5%), purple plates (from methanol), m. p. 272—274° (decomp.) (Found: C, 65·35; H, 5·6; N, 9·8. $C_{23}H_{24}N_3Br$ requires C, 65·4; H, 5·7; N, 9·95%); and 9-p-*methoxyphenyl-* (53%), dark-red plates (from methanol–propan-2-ol), m. p. 230—231° (decomp.) (Found: N, 10·05; Br, 19·65. $C_{21}H_{20}ON_3Br$ requires N, 10·2; Br, 19·5%).

2 : 7-*Diamino*-10-*ethyl*-9-p-*tolylphenanthridinium Bromide* (VII; R = Et, $R^1 = NH_2$, R^2 = *p*-Me·C_6H_4, X = Br).—2 : 7-Dinitro-9-*p*-tolylphenanthridine (12 g.) and ethyl toluene-*p*-sulphonate were heated for 4½ hr. at 185°. The melt was cooled and poured into toluene (250 ml.), and the precipitate extracted with a hot mixture of ethanol (110 ml.), water (80 ml.), and 5N-sulphuric acid (1 ml.). The filtered extract was added to a hot stirred suspension of iron powder (9 g.) in water (300 ml.). This mixture was stirred under reflux for 4 hr. and then cooled, and sodium hydroxide solution (40% w/w; 100 ml.) and toluene (200 ml.) were added with stirring. The toluene layer, containing the pseudo-base ethyl ether, was extracted with dilute hydrochloric acid solution. The pH of the acid extract was raised to 8·5 by ammonia solution, and ammonium bromide added to salt out the *diamino-bromide*. It crystallised (much methanol) in dark-red plates, m. p. 270—271° (Found: N, 10·2; Br, 19·0. $C_{22}H_{22}N_3Br$ requires N, 10·3; Br, 19·6%).

2 : 7-*Diamino*-9-p-iso*propylphenylphenanthridine.*—2 : 7-Dinitro-9-*p*-*iso*propylphenylphenanthridine (8·3 g.) was heated for 1 hr. at 100° with stannous chloride (60 g.) in water (20 ml.), ethanol (80 ml.), and concentrated hydrochloric acid (60 ml.). The resulting solution was

* See Woolfe (refs. 13, 17), for biological testing of these compounds.

[17] Woolfe, *Brit. J. Pharmacol.*, 1956, **11**, 330.

[18] Finzi and Bellavita, *Gazzetta*, 1938, **68**, 77.

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poured on ice and excess of sodium hydroxide solution. The yellow precipitate was extracted with hot ethanol (350 ml.); concentration (to 60 ml.) gave the *diamino*-compound as yellow needles (6 g.), m. p. 222—223° (Found: N, 12·8. $C_{22}H_{21}N_3$ requires N, 12·8%).

10-*Allyl*-2 : 7-*diamino*-9-p-iso*propylphenylphenanthridinium Chloride* (VII; R = Allyl, R^1 = NH_2, R^2 = *p*-Pr^i·C_6H_4, X = Cl).—2 : 7-Diamino-9-*p*-*iso*propylphenylphenanthridine (5·5 g.) was heated with ethyl chloroformate (3·8 ml.) and diethylaniline (8 ml.) in ethanol (200 ml.), and the mixture then diluted with water. 2 : 7-*Bisethoxycarbonylamino*-9-p-iso*propylphenylphenanthridine* (6·3 g.) formed buff-coloured elongated plates (from ethanol), m. p. 216—217° (decomp.) (Found: N, 8·9. $C_{28}H_{29}O_4N_3$ requires N, 8·9%). This compound (6 g.) was heated with allyl iodide (4 ml.) in nitrobenzene (30 ml.) for 3½ hr. at 100°. Addition of ether (30 ml.) to the cooled solution precipitated the *quaternary iodide* (5·3 g.), which was crystallised by dissolution in warm nitrobenzene followed by addition of ether, forming yellow needles, m. p. 212—215° (decomp.) (Found: I, 19·5. $C_{31}H_{34}O_4N_3I$ requires N, 19·9%). The iodide was converted into the corresponding methanesulphonate by metathesis with silver methanesulphonate in aqueous methanol acidified with methanesulphonic acid. It separated as yellow needles, m. p. 210—214° (decomp.). Hydrolysis [15] with 75—80% w/w sulphuric acid at 125—130° gave the required diamine (2·4 g.) which was isolated as the *chloride*, purple plates (from ethanol), m. p. 264° (decomp.) (Found: N, 10·4; Cl, 7·8. $C_{25}H_{26}N_3Cl$ requires N, 10·4; Cl, 8·0%).

Other 10-*allyl*-2 : 7-*bisethoxycarbonylaminophenanthridinium iodides* prepared by similar quaternisation were 9-p-*chlorophenyl*- (for 30 hr.) (71%), yellow needles (from methanol), m. p. 220° (decomp.) (Found: I, 19·8. $C_{28}H_{27}O_4N_3ClI$ requires I, 20·1%); and 9-p-*nitrophenyl*- (for 24 hr.) (44%), yellow needles (from nitrobenzene–ether), decomp. *ca.* 225° (Found: N, 8·5; I, 21·3. $C_{28}H_{27}O_6N_4I$ requires N, 8·7; I, 19·8%). They were converted, as already described, into the 10-*allyl*-2 : 7-*diaminophenanthridinium chlorides*: 9-p-*chlorophenyl*- (44%), purple plates (from ethanol), m. p. 230—232° (decomp.) (Found: N, 10·4; Cl, 9·2. $C_{22}H_{19}N_3Cl_2$ requires N, 10·6; Cl, 9·0%); and 9-p-*nitrophenyl*- (51%), purplish-black plates (from water containing a little ammonium chloride), m. p. 265—267° (decomp.) (Found: N, 13·7; Cl, 8·3. $C_{22}H_{19}O_2N_4Cl$ requires N, 13·75; Cl, 8·7%).

9-p-*Chlorophenyl*-2 : 7-*bisethoxycarbonylaminophenanthridine*.—(a) *p*-Chlorobenzoyl chloride (9·5 g.) was heated with 2-amino-4 : 4′-bisethoxycarbonylaminodiphenyl (17 g.)[12] in chlorobenzene (125 ml.) for 1 hr. to give 2-p-*chlorobenzamido*-4 : 4′-*bisethoxycarbonylaminodiphenyl* (20·1 g.), which formed flat needles, m. p. 121—122°, from a small volume of ethanol (Found: N, 8·7. $C_{25}H_{24}O_5N_3Cl$ requires N, 8·7%). This compound (18 g.) was heated with phosphorus oxychloride (40 ml.) for 1 hr. and the product treated with aqueous ammonia and then twice crystallised from ethanol. The *phenanthridine* (7·8 g.) formed pale-yellow needles, m. p. 222° (Found: N, 8·9. $C_{25}H_{22}O_4N_3Cl$ requires N, 9·05%).

(b) A suspension of 9-*p*-chloro-2 : 7-dinitrophenanthridine (30 g.) was reduced with stannous chloride (220 g.) in concentrated hydrochloric acid (220 ml.) containing 5N-sulphuric acid (20 ml.). The red precipitate was decomposed with sodium hydroxide solution. The *diamine* (10·1 g.) formed yellow needles, m. p. 236—237° (from ethanol) (Found: N, 13·1. $C_9H_{14}N_3Cl$ requires N, 13·1%). This diamine (10 g.) with ethyl chloroformate (7 ml.) in ethanol (300 ml.) and diethylaniline (14 ml.) gave 9-*p*-chlorophenyl-2 : 7-bisethoxycarbonylaminophenanthridine (11·5 g.), as pale yellow needles (from methanol), m. p. 222°, undepressed on admixture with the product obtained by method (a) (Found: N, 9·3%).

2 : 7-*Diamino*-9-p-*chlorophenyl*-10-*methylphenanthridinium Chloride* (VII; R = Me, R^1 = NH_2, R^2 = *p*-Cl·C_6H_4, X = Cl).—The foregoing phenanthridine (4·5 g.) and methyl sulphate (2 ml.), heated in nitrobenzene (15 ml.), gave 9-p-*chlorophenyl*-2 : 7-*bisethoxycarbonylamino*-10-*methylphenanthridinium methyl sulphate* (5 g.), yellow needles (from ethanol), m. p. >250° (Found: N, 6·9. $C_{27}H_{28}O_8N_3SCl$ requires N, 7·1%). Hydrolysis with 75—80% (w/w) sulphuric acid at 125—130°, as previously described, gave the diamine (1·7 g.) isolated as *chloride*, which crystallised from methanol–ethanol as small purple plates, m. p. 253—255° (decomp.; slow heating) (Found: C, 64·5; H, 4·6; N, 11·1. $C_{20}H_{17}N_3Cl_2$ requires C, 64·9; H, 4·6; N, 11·35%).

2 : 7-*Diamino*-10-*ethyl*-9-*nitrophenylphenanthridinium Chlorides* (VII; R = Et, R^1 = NH_2, R^2 = *p*-NO_2·C_6H_4, X = Cl) *and* (VII; R = Et, R^1 = NH_2, R^2 = *m*-NO_2·C_6H_4, X = Cl).—By use of ethyl sulphate and a series of reactions similar to those of the preceding experiment 2 : 7-bisethoxycarbonylamino-9-*p*-nitrophenylphenanthridine [19] was converted into 2 : 7-*diamino*-10-*ethyl*-9-p-*nitrophenylphenanthridinium chloride* (37%). This formed black plates

[19] Walls and Whittaker, *J.*, 1950, 41.

with bronze lustre (from water containing ammonium chloride), m. p. 268—270° (decomp.) (Found, in material heated for 10 hr. at 100°: C, 61·6; H, 5·35; N, 13·3; Cl, 8·8; H_2O, 6·0. $C_{21}H_{19}O_2N_4Cl,H_2O$ requires C, 61·1; H, 5·1; N, 13·6; Cl, 8·6; H_2O, 4·4%. Found, in material dried for 2 hr. at 100°/2 mm.: N, 14·05. $C_{21}H_{19}O_2N_4Cl$ requires N, 14·2%).

The 10-ethyl-*m*-nitrophenyl compound was obtained in the same way (by Dr. J. S. Nicholson). It separated from hydrochloric acid as a *chloride monohydrochloride*, m. p. 240—245° (decomp.) (Found, in material dried at 100°: N, 12·4; H_2O, 6·2. $C_{21}H_{19}O_2N_4Cl,HCl,1\frac{1}{2}H_2O$ requires N, 12·2; H_2O, 5·9%).

2 : 7-*Diamino*-9-p-*nitrophenyl*-10-*propylphenanthridinium Chloride* (VII; R = Pr, R^1 = NH_2, R^2 = *p*-$NO_2{\cdot}C_6H_4$, X = Cl).—This was obtained from 2 : 7-bisethoxycarbonylamino-9-*p*-nitrophenylphenanthridine (24 g.) and propyl toluene-*p*-sulphonate (22 g.) in nitrobenzene (16 ml.) by the reactions described above. The *chloride* (4 g.) crystallised from water in black plates with bronze lustre, m. p. 278—279° (Found : N, 14·1; Cl, 8·9. $C_{22}H_{21}O_2N_4Cl$ requires N, 13·7; Cl, 8·7%).

2 : 7-*Diamino*-9-p-*aminophenyl*-10-*alkylphenanthridinium Chlorides* (VII; R = Et, Pr, or allyl, R^1 = NH_2, R^2 = *p*-$NH_2{\cdot}C_6H_4$, X = Cl).—These salts were obtained by reduction of the corresponding 9-*p*-nitrophenyl salts with ferrous hydroxide by Walls and Whittaker's method.[19] Thus were obtained (from ethanol–propan-2-ol) the 10-*ethyl* compound, dark-red plates, m. p. 290° (decomp.) (Found: N, 15·2; Cl, 9·9. $C_{21}H_{21}N_4Cl$ requires N, 15·3; Cl, 9·7%); the 10-propyl compound, dark-red plates, m. p. 294° (decomp.); and the 10-*allyl* compound, purple prisms, m. p. 245° (decomp.) (Found: N, 14·6; Cl, 9·5. $C_{22}H_{21}N_4Cl$ requires N, 14·8; Cl, 9·4%).

2 : 7-*Diamino*-10-*ethyl*-9-*methylphenanthridinium Bromide* (VII; R = Et, R^1 = NH_2, R^2 = Me, X = Br).—2 : 7-Bisethoxycarbonylamino-9-methylphenanthridine [12] (10 g.) with (*a*) ethyl toluene-*p*-sulphonate (50 g.) for 1 hr. at 150° gave 2 : 7-*bisethoxycarbonylamino*-10-*ethyl*-9-*methylphenanthridinium toluene*-p-*sulphonate*, yellow plates (from methanol) (13·1 g.), m. p. >300° (Found: N, 7·6. $C_{29}H_{33}O_7N_3S$ requires N, 7·4%), or (*b*) ethyl sulphate (10 ml.) in nitrobenzene (15 ml.) at 145° for ¾ hr. gave 2 : 7-*bisethoxycarbonylamino*-10-*ethyl*-9-*methylphenanthridinium ethyl sulphate*, yellow plates (from methanol) (11·8 g.), m. p. >300° (Found: N, 8·2. $C_{24}H_{31}O_8N_3S$ requires N, 8·1%). Either salt on hydrolysis with 75—80% (w/w) sulphuric acid, followed by metathesis to the bromide, gave 2 : 7-*diamino*-10-*ethyl*-9-*methylphenanthridinium bromide*, red prisms (from methanol), m. p. 263—265° (decomp.) (Found: N, 12·4; Br, 23·6. $C_{16}H_{18}N_3Br$ requires N, 12·65; Br, 24·1%).

3-*Amino*-10-*methyl*-9-*phenylphenanthridinium Bromide* (VIII; R = Ph, X = Br).—3-Nitro-9-phenylphenanthridine [21] heated with methyl sulphate in nitrobenzene gave a quantitative yield of 10-*methyl*-3-*nitro*-9-*phenylphenanthridinium methyl sulphate*, yellow plates (from ethanol), m. p. 295—297° (decomp.) (Found: N, 6·35. $C_{21}H_{18}O_6N_2S$ requires N, 6·55%). Reduction with iron in acidified aqueous alcohol solution yielded the corresponding amino-compound. This was isolated as the *bromide*, orange-coloured plates (from water containing a little ammonium bromide) (68%), m. p. 193° (decomp.) (Found: N, 7·7; Br, 22·2. $C_{20}H_{17}N_2Br$ requires N, 7·65; Br, 21·9%).

3-*Ethoxycarbonylamino*-9-p-*nitrophenylphenanthridine*.—2-Acetamido-5-ethoxycarbonylaminodiphenyl [21] (16 g.) was hydrolysed with 2·5N-hydrochloric acid in aqueous ethanol solution. The crude 2-amino-5-ethoxycarbonylaminodiphenyl isolated was stirred with *p*-nitrobenzoyl chloride (13 g.) in pyridine (20 ml.) at 20—25° for 1½ hr. and then at 100° for 1 hr. The product was precipitated by dilute acid and crystallised from ethanol. 5-*Ethoxycarbonylamino*-2-p-*nitrobenzamidodiphenyl* (16·4 g.) formed plates, m. p. 183—184° (Found: N, 10·3. $C_{22}H_{19}O_5N_3$ requires N, 10·35%). The compound (16 g.) was heated with phosphorus oxychloride (13 ml.) in nitrobenzene (20 ml.) to give 3-*ethoxycarbonylamino*-9-p-*nitrophenylphenanthridine* (8·4 g.), yellow plates (from aqueous pyridine), m. p. >320° (Found: N, 10·9. $C_{22}H_{17}O_4N_3$ requires N, 10·85%).

3-*Amino*-10-*methyl*-9-p-*nitrophenylphenanthridinium Bromide* (VIII; R = *p*-$NO_2{\cdot}C_6H_4$, X = Br).—The foregoing compound (4 g.) was heated with methyl sulphate (3·3 ml.) in nitrobenzene (17 ml.) to give the 10-*methyl-phenanthridinium methyl sulphate* (4 g.), yellow plates (from nitrobenzene), m. p. 246—248° (decomp.) (Found: N, 8·2. $C_{24}H_{23}O_6N_3S$ requires N, 8·2%). This compound was hydrolysed with 75—80% (w/w) sulphuric acid as in previous examples, and the

[20] B.P. 679,148.
[21] Mamalis and Petrow, *J.*, 1950, 703.

XUM

TABLE 1. *Pyrimidinylphenanthridines* (III) *prepared from the salts* (VII).

Substituent in (III)			X in (VII)		Yield		Found, %			Required, %			
R	R^1	R^2	X		(%)	Formula	N	I	H_2O	N	I	H_2O	Description
NH_2	Me	Ph	I [a]	Br	73	$C_{26}H_{26}N_6I_2,2H_2O$ [b]	12·1	34·8	4·7	11·8	35·65	5·05	Small red plates [c]
NH_2	Me	Ph	I [a,d]	—	67	$C_{26}H_{26}N_6I_2,2H_2O$ [b]	—	—	—	—	—	—	,, ,, [e]
NH_2	Me	Ph	CH_3SO_3 [e]	Br	—	$C_{28}H_{32}O_6N_6S_2,2H_2O$ [b]	13·15	—	6·3	12·95	—	5·55	Elongated red plates [f]
NH_2	Me	Ph	Br [g]	Br	65	$C_{26}H_{26}N_6Br_2$ [h]	14·2	—	—	14·4	—	—	,, ,,
NH_2	Et	Ph	I	Br	72	$C_{27}H_{28}N_6I_2$	12·0	38·0	—	12·2	37·4	—	Red plates [c]
NH_2	Et	Ph	CH_3SO_3 [i]	Br	61	$C_{29}H_{34}O_4N_6S_2,H_2O$ [b]	13·1	—	3·1	13·0	—	2·8	,, [c]
NH_2	Et	Ph	Cl	Br	63	$C_{27}H_{28}N_6Cl_2,H_2O$ [b,k]	16·2	—	2·9	16·0	—	3·4	,, [c]
H	Me	p-$NO_2{\cdot}C_6H_4$	I	Br(Cl)	83	$C_{26}H_{24}O_4N_6I_2,2H_2O$ [b]	11·1	33·6	4·7	11·3	34·2	4·9	Small brown plates [l]
H	Me	p-$NH_2{\cdot}C_6H_4$	I [m]	—	64	$C_{26}H_{26}N_6I_2$	12·5	36·9	—	12·4	37·6	—	Brick-red microcrystals [l]
NH_2	Me	p-$NO_2{\cdot}C_6H_4$	I	Br	54	$C_{26}H_{25}O_2N_7I_2$	13·8	34·4	—	13·6	35·2	—	Small red plates [n]
NH_2	Me	p-$NO_2{\cdot}C_6H_4$	Cl	Br	45	$C_{26}H_{25}O_2N_7Cl_2,2H_2O$ [b,o,p]	17·3	—	2·4	17·1	—	3·1	,, ,, [c]
NH_2	Me	p-$NO_2{\cdot}C_6H_4$	CH_3SO_3	Br	—	$C_{28}H_{31}O_8N_7S_2,2H_2O$ [b]	13·9	—	5·6	14·1	—	5·2	,, ,, [c]
NH_2	Me	p-$NH_2{\cdot}C_6H_4$	Br [m,q]	—	43	$C_{26}H_{27}N_7Br_2$ [r,s]	16·6	—	—	16·4	—	—	Red microcrystals [c]
NH_2	Et	p-$NO_2{\cdot}C_6H_4$	I	Br	55	$C_{27}H_{27}O_2N_7I_2,2H_2O$ [b]	12·8	—	4·2	12·7	—	4·7	Minute red plates [c]
NH_2	Et	p-$NH_2{\cdot}C_6H_4$	Br [m]	—	38	$C_{27}H_{29}N_7Br_2,2H_2O$ [t]	15·2	—	5·0	15·15	—	5·55	Small red plates [c]
NH_2	Me	m-$NH_2{\cdot}C_6H_4$	Br [u]	Br	20	$C_{26}H_{27}N_7Br_2$	16·1	—	—	16·4	—	—	Red solid [v]
NH_2	Et	m-$NH_2{\cdot}C_6H_4$	Br [u]	Br [w]	22	$C_{27}H_{29}N_7Br_2,H_2O$ [t,x]	16·0	—	2·6	15·6	—	2·6	Red microcrystals [c]
NH_2	Me	p-Me·C_6H_4	I	Br	70	$C_{27}H_{28}N_6I_2$	12·0	—	36·3	12·2	36·8	—	Small red plates [c]
NH_2	Me	p-Me·C_6H_4	Cl	Br	64	$C_{27}H_{28}N_6Cl_2,6H_2O$ [t]	13·6	—	17·1	13·6	—	17·55	,, ,, [c]
NH_2	Me	p-$Pr^i{\cdot}C_6H_4$	I	Br	78	$C_{29}H_{32}N_6I_2$	11·9	36·0	—	11·7	35·4	—	Red microcrystals [v]
NH_2	Me	p-$Pr^i{\cdot}C_6H_4$	Cl	Br	65	$C_{29}H_{32}N_6Cl_2,6H_2O$ [t]	13·3	—	16·3	13·1	—	16·8	,, ,, [c]
NH_2	Allyl	p-$Pr^i{\cdot}C_6H_4$	I	Cl	65	$C_{31}H_{36}N_6I_2$	11·25	33·5	—	11·3	34·1	—	,, ,, [v]
NH_2	Me	p-Cl·C_6H_4	I	Cl	64	$C_{26}H_{25}N_6ClI_2$	11·9	37·4	—	11·8	37·75	—	,, ,, [v]
NH_2	Me	p-Cl·C_6H_4	Cl	Cl	51	$C_{26}H_{25}N_6Cl_2,6H_2O$ [t]	13·2	—	16·7	13·2	—	17·0	,, ,, [c]
NH_2	Me	p-MeO·C_6H_4	I	Br	69	$C_{27}H_{28}ON_6I_2$	12·3	35·8	—	11·9	36·0	—	Small red plates [c]
NH_2	Me	p-MeO·C_6H_4	Cl	Br	62	$C_{27}H_{28}ON_6Cl_2,6H_2O$ [t]	13·1	—	16·5	13·3	—	17·1	,, ,, [c]
NH_2	Me	p-Dimethylamino-styryl	I	Br	70	$C_{30}H_{33}N_7I_2$	12·9	33·4	—	13·15	34·1	—	Small purple-black plates [n]
NH_2	Me	p-Dimethylamino-styryl	Cl	Br	59	$C_{30}H_{33}N_7Cl_2,4H_2O$ [t]	15·6	—	11·1	15·5	—	11·35	,, ,, [n]
NH_2	Et	p-Dimethylamino-styryl	I	Cl	74	$C_{31}H_{39}N_7I_2$	12·7	33·7	—	12·9	33·5	—	,, ,, [n]
NH_2	Me	Me	I	Br	79	$C_{21}H_{24}N_6I_2$	13·5	42·0	—	13·7	41·4	—	Red plates [v]
NH_2	Me	Me	CH_3SO_3	Br	65	$C_{22}H_{30}N_6O_6S_2$	14·4	—	5·8	14·3	—	6·1	Red needles [c]
H	Me	Ph	I [y]	Br	82	$C_{25}H_{23}N_5I_2$	10·5	37·5	—	10·6	38·4	—	Yellow needles [l]
H	Me	Ph	CH_3SO_3 [z]	Br	62	$C_{28}H_{31}O_6N_5S_2,H_2O$ [aa]	11·0	—	6·2	11·0	—	5·7	Yellow plates [ab]

[a] M. p. >300° but shrinking occurred at 281°. [b] Compound dried at 100°. [c] From methanol. [d] Prepared from 7-amino-10-methyl-2-nitro-9-phenylphenanthridinium chloride. The intermediate condensation product was reduced with ferrous hydroxide. M. p. undepressed by admixture with previous compound. Also, the two compounds had identical infrared spectra and paper chromatograms (developed in butanol–water). [e] M. p. 238—240° (decomp.). [f] From methanol–ethylene dichloride. [g] M. p. 299° (decomp.). [h] Found: Br, 27·2. $C_{26}H_{26}N_6Br_2$ requires Br, 27·5%. [i] From water. [j] M. p. 245° (decomp.). [k] The compound formed a tetrahydrate on exposure to air (Found: N, 14·7; H_2O, 12·6. $C_{27}H_{28}N_6Cl_2,4H_2O$ requires N, 14·5; H_2O, 12·4%). [l] From water containing a little potassium iodide. [m] Prepared by ferrous hydroxide reduction of the foregoing nitropyrimidinylphenanthridine after metathesis with silver methanesulphonate. [n] From aqueous methanol. [o] Found: C, 53·9; H, 5·2. $C_{26}H_{25}O_2N_7Cl_2,2H_2O$ requires C, 54·0; H, 5·1%. [p] The compound formed a tetrahydrate on exposure to air (Found: H_2O, 12·2. $C_{26}H_{25}O_2N_7Cl_2,4H_2O$ requires H_2O, 11·8%). [q] The compound was also prepared from the mixture obtained from the nitropyrimidinylphenanthridine preparation. Metathesis with silver methanesulphonate was first carried out and the

from the mixture obtained from the nitropyrimidinylphenanthridine preparation. Metathesis with silver methanesulphonate was first carried out and the

filtrate, obtained on separation of the silver salts, was then reduced with ferrous hydroxide. The product was twice crystallised from methanol (Found, in compound dried at 100° and then exposed to air: N, 15·3; H_2O, 6·0. $C_{26}H_{27}N_7Br_2,2H_2O$ requires N, 15·5; H_2O, 5·7%). [r] Found: Br, 26·1. $C_{26}H_{27}N_7Br_2$ requires Br, 26·8%. [s] This compound formed a *dihydrate* on exposure to air for 2 days. Found: C, 49·4; H, 5·0; N, 15·6; H_2O, 6·3. $C_{26}H_{27}N_7Br_2,2H_2O$ requires C, 49·3; H, 4·9; N, 15·5; H_2O, 5·7%. [t] Compound dried at 100° and then exposed to air. [u] Prepared by Dr. J. S. Nicholson, from 2 : 7-diamino-10-methyl-9-*m*-nitrophenylphenanthridinium chloride. The intermediate nitropyrimidinylphenanthridine, isolated as a dichloride, was reduced with ferrous hydroxide. [v] From aqueous ethanol. [w] M. p. 263—265° (decomp.). [x] Found: Br, 25·7. $C_{27}H_{29}N_7Br_2,H_2O$ requires Br, 25·4%. [y] M. p. 301° (decomp.). [z] M. p. 303° (decomp.). [aa] Found: C, 52·6; H, 5·8. $C_{28}H_{31}O_6N_5S_2,H_2O$ requires C, 53·0; H, 5·5%. [ab] From ethanol.

TABLE 2. *Pyrimidinylphenanthridines* (V) *prepared from the bromides* (VIII; X = Br).

Substituent R	X	M. p. (decomp.)	Yield (%)	Formula	Found, % N	I	H_2O	Required, % N	I	H_2O	Description
Me	I	285°	85	$C_{21}H_{23}N_5I_2$	11·8	43·0	—	11·7	42·4	—	Small yellow plates [a]
Me	CH_3SO_3	306—308°	73	$C_{28}H_{29}O_6N_5S_2,H_2O$ [b]	12·5	—	2·9	12·6	—	3·25	Yellow plates [c]
Ph	I	293—294°	79	$C_{26}H_{25}N_5I_2$	10·8	38·5	—	10·6	—	38·4	Yellow needles [d]
Ph	CH_3SO_3	232°	66	$C_{28}H_{31}O_6N_5S_2$	11·6	—	—	11·7	—	—	Yellow needles [e]
p-NH_2·C_6H_4 [e]	I	295°	68	$C_{26}H_{26}N_6I_2$	12·5	38·2	—	12·3	37·5	—	Orange prisms [d]

[a] From water containing a little potassium iodide. [b] Compound dried at 100° and then exposed to air. [c] From methanol. [d] From water. [e] Prepared from the *p*-nitrophenyl compound; the intermediate 3-(2-amino-6-methyl-4-pyrimidinylamino)-9-*p*-nitrophenylphenanthridine 10 : 1′-dimethochloride was reduced in aqueous solution with ferrous hydroxide.

TABLE 3. *Dipyrimidinylphenanthridines* (IV).

Substituent R	X	Starting material	Yield (%)	Formula	Found, % N	I	H_2O	Required, % N	I	H_2O	Description
Ph	I	VII; R = Me, R^1 = NH_2, R^2 = Ph, X = Br	78	$C_{32}H_{34}N_9I_3$	13·8	41·3	—	13·6	41·7	—	Yellow plates [a]
Ph	Br	" " " "	—	$C_{32}H_{34}N_9Br_3$ [b]	15·9	—	—	16·1	—	—	Yellow needles [c]
p-NO_2·C_6H_4	I	VII; R = Me, R^1 = NH_2, R^2 = *p*-NO_2·C_6H_4, X = Br	82	$C_{32}H_{32}O_2N_{10}I_3,H_2O$ [d]	14·0	37·1	3·8	13·9	37·8	3·6	Orange microcrystals [c]
p-NH_2·C_6H_4	I [f]	—	79	$C_{32}H_{33}N_{10}I_3$	15·2	40·2	—	14·9	40·5	—	Small red plates [c]
p-Me·C_6H_4	I	III; R = NH_2, R^1 = Me, R^2 = *p*-Me·C_6H_4, X = Cl	78	$C_{33}H_{36}N_9I_3$	13·8	40·1	—	13·4	40·6	—	Orange microcrystals [a]
p-Me·C_6H_4	Cl	" " " "	—	$C_{33}H_{36}N_9Cl_3,6H_2O$ [g]	16·5	—	13·9	16·3	—	14·0	" " [a]
p-Pr^i·C_6H_4	I	III; R = NH_2, R^1 = Me, R^2 = *p*-Pr^i·C_6H_4, X = Cl	81	$C_{35}H_{40}N_9I_3$	13·3	39·0	—	13·0	39·4	—	" "
p-Pr^i·C_6H_4	Cl	" " " "	—	$C_{35}H_{40}N_9Cl_3,4H_2O$ [g]	16·2	—	9·5	16·45	—	9·45	" "
p-Cl·C_6H_4	Cl	III; R = NH_2, R^1 = Me, R^2 = *p*-Cl·C_6H_4, X = Cl	75	$C_{33}H_{33}N_9Cl_4,6H_2O$ [g]	15·8	—	13·1	15·9	—	13·6	" "
p-MeO·C_6H_4	I	III; R = NH_2, R^1 = Me, R^2 = *p*-MeO·C_6H_4, X = Cl	80	$C_{33}H_{36}ON_9I_3$	13·2	39·2	—	13·2	39·9	—	" "
p-MeO·C_6H_4	Cl	" " " "	—	$C_{33}H_{36}ON_9Cl_3,2H_2O$ [h]	17·6	—	5·5	17·6	—	5·0	" "
Me	I	VII; R = Me, R^1 = NH_2, R^2 = Me, X = Br	83	$C_{27}H_{32}N_9I_3$	14·3	44·3	—	14·6	44·1	—	Small red plates [a]
Me	Cl	" " "	71	$C_{27}H_{32}N_9Cl_3,2H_2O$ [g,i]	20·1	—	6·2	20·2	—	5·8	" " [a]

[a] From water containing a little potassium iodide. [b] Found: Br, 30·1. $C_{32}H_{34}N_9Br_3$ requires Br, 30·6%. [c] From methanol. [d] Compound dried at 100°. [e] From water. [f] Prepared by reduction with ferrous hydroxide of the previous nitro-compound. [g] Dried at 100° and then exposed to air. [i] Found: Cl, 16·5. $C_{27}H_{32}N_9Cl_3,2H_2O$ requires Cl, 17·05%.

product isolated as 3-*amino*-10-*methyl*-9-p-*nitrophenylphenanthridinium bromide* (from water containing a little ammonium bromide), yellow plates, m. p. 230° (decomp.) (Found: N, 10·4; Br, 19·2. $C_{20}H_{16}O_2N_3Br$ requires N, 10·2; Br, 19·5%).

Preparation of Pyrimidinylphenanthridines (III) *and* (V).

The phenanthridinium salt and 2-amino-4-chloro-1 : 6-dimethylpyrimidinium iodide (II) [23] (1 mol.) were heated in water containing hydrochloric acid (1 equiv.) for 45—60 min. The progress of the reaction was followed by potentiometric titration of the acid formed with sodium hydroxide solution. In one case (preparation of III; R = H, R^1 = Me, R^2 = Ph) the rate of formation of this acid was greater when 1 equiv. of acid was already present. In most preparations the product separated during this heating period, otherwise the solution was cooled. The solid, of mixed anion content, was collected and washed with water. It was then characterised, after metathesis, as follows: (*a*) the solid was dissolved in hot water and excess of potassium iodide added; the precipitated di-iodide was characterised as such, or converted by heating with a silver salt in aqueous or aqueous alcoholic solution or suspension into a more water-soluble salt or (*b*) the solid was refluxed in aqueous suspension with silver chloride, and a salt, which could be characterised, was then precipitated from the filtered solution. The compounds were purified by crystallisation from water, methanol, or ethanol, or mixtures of these. The *compounds* listed in Tables 1 and 2 were thus prepared. All m. p.s were >275° unless otherwise stated.

Preparation of Pyrimidinylphenanthridines (IV).

Attempted preparations of compounds of type (IV) by reaction of the phenanthridinium compound with 2 mols. of the pyrimidinium iodide (II) in water or in water containing 1 or 2 equivs. of hydrochloric acid gave products of indefinite melting point and analysis. The latter indicated, however, a higher nitrogen content than that expected for a monocondensation product.

The reaction proceeded smoothly in phenol. The phenanthridinium compound and the pyrimidine (II) (2 mols.) were heated in phenol (30—50 mols.) for 1 hr. at 140°. The cooled solution was poured into an excess of ether; the product quickly solidified, and was then well boiled out with ether to remove traces of phenol. Potassium iodide was added to an aqueous solution to precipitate the tri-iodide, which was crystallised from water. The bis-compound could also be prepared from 1 mol. of a monocondensation product (III; R = NH_2) and 1 mol. of the pyrimidine (II) in phenol for 1 hr. at 140°. The *products* are detailed in Table 3 (all m. p.s were >300°).

Preparation of the Pyrimidinylphenanthridine (VI).

2 : 7-*Diacetamido*-9-p-(2-*amino*-6-*methyl*-4-*pyrimidinylamino*)*phenylphenanthridine* 10 : 1′-*Dimethiodide*.—Prepared by heating 2 : 7-diacetamido-9-*p*-aminophenyl-10-methylphenanthridinium chloride (4 g.) [22] and the pyrimidine (II) in phenol for 1 hr. at 140°, the *iodide* formed brownish-red prisms (from water containing a little potassium iodide), m. p. >300° (Found: N, 13·0; I, 32·3. $C_{30}H_{31}O_2N_7I_2$ requires N, 12·65; I, 32·65%).

2 : 7-*Diamino*-9-p-(2-*amino*-6-*methyl*-4-*pyrimidinylamino*)*phenylphenanthridine* 10 : 1′-*Dimethiodide* (VI).—The foregoing compound was heated with boiling 2N-hydrochloric acid (45 min.). Adjustment of pH to 7 and addition of potassium iodide gave the required diamine as the *iodide* (3·4 g.), small dark-red prisms (from water containing a little potassium iodide), m. p. >300° (Found: N, 14·1; I, 36·2. $C_{26}H_{27}N_7I_2$ requires N, 14·2; I, 36·75%). The *methanesulphonate*, prepared from the iodide by metathesis, formed small purple prisms (from ethanol), m. p. 290° (decomp., slow heating) (Found, in compound dried at 100° and then exposed to air: N, 14·5; H_2O, 5·9. $C_{28}H_{33}O_6N_7S_2.2H_2O$ requires N, 14·8; H_2O, 5·4%).

The author thanks Dr. D. A. Peak and the late Dr. W. F. Short for their help and encouragement, and Mr. P. N. Calcraft for technical assistance.

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Boots Pure Drug Co. Limited, Nottingham. [*Received, July 5th,* 1957.]

[22] Morgan and Walls, *J.*, 1932, 2225.
[23] Ainley *et al.*, *J.*, 1953, 59.

290. *Dephenylation Reactions of Phenylboron Acids and Esters.*

By E. W. Abel, W. Gerrard, and M. F. Lappert.

Dephenylation (B–C cleavage), at high temperatures, of diphenylboronous acid and esters, $Ph_2B{\cdot}Y$ (Y = OH or OR), and of phenylboronic acid and esters, $Ph{\cdot}BY_2$, are described.

Continuing the study of reactions of phenylboron acids,[1–5] we now show that at temperatures approaching 200° phenylboronic acid affords benzene and metaboric acid, whereas diphenylboronous acid accordingly gives benzene and phenylboronic anhydride. As the latter anhydride readily gives the acid with water, complete dephenylation of boron occurred when diphenylboronous acid was heated with water. Analogously, when an alkyl diphenylboronite, $Ph_2B{\cdot}OR$, was heated with the corresponding alcohol, the ester of phenylboronic acid or of boric acid was formed according to the proportion of alcohol. When R in the alcohol was different, a mixture of the two alkyl borates, instead of the desired mixed borate, was obtained. Experiments with optically active 1-methylheptyl compounds show that there is no C–O fission.

At 200° the esters of diphenylboronous acid themselves were much more stable and slowly disproportionated rather than undergoing dephenylation by the elimination of olefin. In one example triphenylboron was isolated. Dimethyl phenylboronate slowly disproportionated to trimethyl borate and methyl diphenylboronite. The amount of tri-*n*-butyl borate was slowly reduced when this ester was heated (200°) with *n*-butyl diphenylboronite, and di-*n*-butyl phenylboronate was isolated.

Pyrolysis of *n*-octyl diphenylboronite at 340° gave phenylboronic anhydride (presumably from the production of the acid on treatment with water), benzene, and octene (apparently a mixture of oct-2- and -3-ene as judged from the absence of vinyl absorption in the infrared spectrum, a similar rearrangement having been postulated for the dehydration of octan-1-ol by phosphoric acid [6]).

These results are of fundamental interest in the search for " boron polymers " stable to high temperatures. The dephenylation reactions have correlation with the dephenylation (desilylation) of certain phenylsilanes.[7]

Experimental

Preparations and Procedures.—Phenylboronic acid was prepared by Bean and Johnson's method,[8] diphenylboronous acid by that of Abel *et al.*[9] Dimethyl phenylboronate was obtained by Dandegaonker, Gerrard, and Lappert's procedure,[4] the alkyl diphenylboronites by a method described by us previously,[2] and tri-*n*-butyl borate according to Johnson and Tompkins.[10] Analytical techniques have been described previously.[2,3] Rotatory powers are recorded for $l = 10$ cm. Unless otherwise stated, reactions were carried out in sealed tubes.

Pyrolysis of Phenylboronic Acid.—The acid (6·89 g.) was heated at 200° for 25 hr. Subsequently, benzene (4·30 g., 98%), b. p. 80°, n_D^{20} 1·4992, was removed at 20°/15 mm. and trapped at −80°. Metaboric acid (2·60 g., 100%) (Found: B, 23·8. Calc. for HO_2B: B, 24·5%) remained as a pale grey glass.

[1] Lappert, *Chem. Rev.*, 1956, **56**, 959.
[2] Abel, Gerrard, and Lappert, *J.*, 1957, 112.
[3] *Idem*, *J.*, 1957, 3833.
[4] Dandegaonker, Gerrard, and Lappert, *J.*, 1957, 5051.
[5] Ainley and Challenger, *J.*, 1930, 2171; Challenger and Richards, *J.*, 1934, 405; Letsinger and Remes, *J. Amer. Chem. Soc.*, 1955, **77**, 2489.
[6] Whitmore and Herndon, *ibid.*, 1933, **55**, 3428; Waterman and Te Nuyl, *Rec. Trav. chim.*, 1932, **51**, 533; Abel, Gerrard, and Lappert, *Chem. and Ind.*, 1958, 158.
[7] Eaborn, *J.*, 1953, 3148, and subsequent papers.
[8] Bean and Johnson, *J. Amer. Chem. Soc.*, 1932, **54**, 4415.
[9] Abel, Dandegaonker, Gerrard, and Lappert, *J.*, 1956, 4697.
[10] Johnson and Tompkins, *Org. Synth.*, 1933, **13**, 16.

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Pyrolysis of Diphenylboronous Acid.—The acid (6·86 g.) was heated at 175° for 8 hr. Benzene (2·79 g., 96%), n_D^{20} 1·5033 (m. p. of dinitrobenzene 90°), was removed and trapped at −80°. The residue of phenylboronic anhydride (3·79 g., 97%) (Found: B, 10·5. Calc. for C_6H_5OB: B, 10·4%) recrystallized as phenylboronic acid from hot water; subsequent dehydration produced a pure sample of the anhydride, m. p. 216°.

Interaction of Diphenylboronous Acid and Water.—The acid (5·50 g.) and water (1·09 g.) were heated at 175° for 20 hr. Removal of benzene (4·61 g., 98%), n_D^{20} 1·5029 (m. p. of dinitrobenzene 89°) was effected at 20°/10 mm., to leave boric acid (1·90 g., 100%) (Found: B, 17·2. Calc. for H_3O_3B: B, 17·4%) as a fine white powder.

Interaction of 1-*Methylheptyl Diphenylboronite and* 1-*Methylheptyl Alcohol.*—The ester (4·47 g.), α_D^{20} −3·71° (from ROH, α_D^{20} +6·22°), and alcohol (1·98 g.), α_D^{20} +6·22°, were heated at 200° for 12 hr. Distillation gave a forerun (0·54 g.), b. p. 25—130°/0·05 mm., and di-(+)-1-methylheptyl phenylboronate (4·71 g., 90%), b. p. 130°/0·05 mm., n_D^{20} 1·4680, α_D^{20} +11·50° (Found: B, 3·11. Calc. for $C_{22}H_{39}O_2B$: B, 3·13%). Benzene (1·14 g., 95%), n_D^{20} 1·4993, b. p. 80°, was trapped at −80° during the distillation.

Interaction of Alkyl Diphenylboronite and Alcohols.—(*a*) The methyl ester (6·19 g.) and methanol were heated at 200° for 50 hr. Vapour-phase chromatography of the product revealed methyl borate and benzene only. A quantitative infrared analysis of the mixture revealed 59% of benzene by volume, corresponding closely to a mixture of methyl borate (1 mol.) and benzene (2 mols).

(*b*) The *n*-butyl ester (6·35 g.) and butan-1-ol were heated at 200° for 50 hr. Distillation gave tri-*n*-butyl borate (5·72 g., 94%), b. p. 106°/8 mm., n_D^{20} 1·4097 (Found: B, 4·8. Calc. for $C_{12}H_{27}O_3B$: B, 4·7%). Benzene (4·16 g., 100%), b. p. 80°, n_D^{20} 1·4990, was trapped at −80° during the distillation, and there was a solid residue (0·17 g.).

(*c*) (−)-1-Methylheptyl diphenylboronite (5·84 g.), α_D^{20} −3·71° (from ROH, α_D^{20} +6·22°), and (+)-octan-2-ol (5·18 g.), α_D^{20} 6·22°, were heated at 200° for 100 hr. Distillation gave a forerun (1·33 g.), b. p. 25—140°/0·05 mm., and (+)-1-methylheptyl borate (6·33 g., 80%), b. p. 140°/0·05 mm., n_D^{20} 1·4297, α_D^{20} +19·86° (Found: B, 2·8. Calc. for $C_{24}H_{51}O_3B$: B, 2·7%). During the distillation benzene (2·93 g., 95%), b. p. 80°, n_D^{20} 1·4999 (m. p. of dinitrobenzene, 90°), was trapped at −80°.

Rates of Dephenylation of Alkyl Diphenylboronites.—Samples (*ca.* 0·2 g.) of the ester (1 mol.) and the alcohol (2 mols.) were sealed and heated at 200°. The rate of dephenylation was followed by infrared analysis (for benzene) after stated times; the results are shown in Tables 1 and 2.

TABLE 1. Bu^n *ester.*

Time (hr.)	1	2	4	8	20	25	30	40	45
Reaction (%)	11	16	32	51	71	79	86	97	100

TABLE 2. *n*-C_6H_{13}·CHMe *ester.*

Time (hr.)	1	2	4	6	8	20	30	50
Reaction (%)	8	15	25	34	41	66	72	95

Interaction of n-*Octyl Diphenylboronite and Butan-*1-*ol.*—The ester (10·37 g.) and alcohol (5·22 g.) were heated at 200° for 50 hr. Distillation gave tri-*n*-butyl borate (5·16 g., 96%), b. p. 74°/0·01 mm., n_D^{20} 1·4097 (Found: B, 4·6%), and tri-*n*-octyl borate (4·21 g., 90%), b. p. 164°/0·01 mm., n_D^{20} 1·4361 (Found: B, 2·9%). Benzene (5·48 g., 100%), b. p. 80°, n_D^{20} 1·4970, was trapped at −80° during the distillation.

Pyrolysis of Ethyl Diphenylboronite.—The ester (7·04 g.) was heated at 200° for 100 hr. Distillation then gave diethyl phenylboronate (1·07 g.), b. p. 43°/0·05 mm., n_D^{20} 1·4800 (Found: B, 6·2. Calc. for $C_{10}H_{15}O_2B$: B, 6·1%), ethyl diphenylboronite (3·37 g.), b. p. 92°/0·05 mm., n_D^{20} 1·5540 (Found: B, 5·2. Calc. for $C_{14}H_{15}OB$: B, 5·2%), and triphenylboron (2·00 g.), b. p. 154°/0·05 mm. (Found: B, 4·70. Calc. for $C_{18}H_{15}B$: B, 4·56%). Trapped at −80° was a mixture (0·22 g.) of benzene and triethyl borate (detected by vapour-phase chromatography).

Pyrolysis of n-*Octyl Diphenylboronite.*—The ester (16·28 g.) was heated at 340°, under a reflux air-condenser (6″), and volatile matter was allowed to distil off. After 130 hr. no further change took place. Vapour-phase chromatography of the volatile matter revealed benzene and octene (by comparison with authentic samples), and a quantitative infrared analysis showed them to be present in equimolar proportions. The tar-like residue (5·98 g.) (Found: B,

10·2%) was extracted with boiling water, and the hot aqueous solution decolorized with charcoal. On cooling, phenylboronic acid crystallized, and after dehydration at 110° for 10 hr. phenylboronic anhydride (4·2 g.) (Found: B, 10·3%), m. p. 214°, was obtained.

Pyrolysis of Dimethyl Phenylboronate.—The ester (4·61 g.) was heated at 200° for 100 hr. Distillation afforded dimethyl phenylboronate (3·66 g.), n_D^{20} 1·4953 (Found: B, 7·2. Calc. for $C_8H_{11}O_2B$: B, 7·2%), and methyl diphenylboronite (0·49 g.), n_D^{20} 1·5691 (Found: B, 5·42. Calc. for $C_{13}H_{13}OB$: B, 5·53%) (authentic infrared spectrum). Trapped at −80° during the distillation was trimethyl borate (0·21 g.) (Found: B, 9·4. Calc. for $C_3H_9O_3B$: B, 9·9%). There was a residue (0·14 g.).

Interaction of n-*Butyl Diphenylboronite and Tri*-n-*butyl Borate.*—*n*-Butyl diphenylboronite (5·53 g.) and tri-*n*-butyl borate (5·36 g.) were heated at 200° for 100 hr. Distillation gave tri-*n*-butyl borate (3·71 g.), b. p. 110°/10 mm., n_D^{20} 1·4138 (Found: B, 4·8%), di-*n*-butyl phenylboronate (3·51 g.), b. p. 126°/10 mm., n_D^{20} 1·4773 (authentic infrared spectrum) (Found: B, 4·7. Calc. for $C_{14}H_{23}O_2B$: B, 4·6%), and *n*-butyl diphenylboronite (3·21 g.), b. p. 156°/9 mm., n_D^{20} 1·5374 (Found: B, 4·7. Calc. for $C_{14}H_{19}OB$: B, 4·54%). Benzene (0·09 g.) was trapped at −80° during the distillation and there was a residue (0·28 g.).

Facilities for infrared measurements were made available in the National College of Rubber Technology (Northern Polytechnic), and we thank Mr. H. Pyszora for the measurements. One of us (E. W. A.) thanks the Courtauld Scientific and Educational Trust Fund for a scholarship.

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[*Received, July 23rd,* 1957.]

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291. *The Infrared Spectra of the Methylsilyl Halides and Related Compounds.*

By E. A. V. EBSWORTH, M. ONYSZCHUK, and N. SHEPPARD.

Infrared spectra have been recorded of the compounds $(CH_3{\cdot}SiH_2)_nX$; X is CH_3, F, Cl, Br, I, and NC when $n = 1$; X is O or S when $n = 2$; and X is N when $n = 3$. Particular attention has been paid to the assignment of frequencies to the vibrations of the SiH_2 group and to the Si–X bond-stretching modes. The ranges recorded for the SiH_2 frequencies were 2200—2140 (νSiH); 980—940 (SiH_2 bend. or scissors); 955—875 (SiH_2 wag.); 740—630 (SiH_2 twist.); and 520—460 cm.$^{-1}$ (SiH_2 rock.). The frequencies of the SiH_2 wagging and bending modes increase approximately linearly with the electronegativity of X.

CONSIDERABLE interest has been shown in the characteristic frequencies of vibrations of the SiH_3, SiH_2, and SiH groups as observed in complex molecules.[1-4] Several series of compounds have recently been prepared in this laboratory containing the groupings $CH_3{\cdot}SiH_2{-}$, $(CH_3)_2SiH{-}$, and $(CH_3)_3Si{-}$ bound to various atoms, and their infrared spectra have been recorded and compared. The purpose of this paper is to interpret the spectra of the monomethylsilyl compounds in terms of the vibrations of these molecules. In the spectra of the simpler compounds vapour-phase band-contour data often make it possible to classify the absorption frequencies reliably in terms of the symmetry species of the corresponding vibrations.

A second paper will deal with the spectra of derivatives of more highly methylated silyl groups.

[1] West and Rochow, *J. Org. Chem.*, 1953, **18**, 303.
[2] Kaye and Tannenbaum, *ibid.*, p. 1750.
[3] Opitz, Peake, and Nebergall, *J. Amer. Chem. Soc.*, 1956, **78**, 292.
[4] Westermark, *Acta Chem. Scand.*, 1955, **9**, 947.

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Experimental

The preparation of the compounds is described elsewhere.[5, 6, 7] The spectra were studied in the region 4000—400 cm.$^{-1}$ by use of a Perkin-Elmer model 21 double-beam spectrometer fitted with 60° calcium fluoride, sodium chloride, or potassium bromide prisms. The substances were examined in the vapour phase, and their purities were checked by vapour-pressure measurements. The only impurity detected spectroscopically was the analogous methylsilyl ether $(CH_3{\cdot}SiH_2)_2O$; very small concentrations of this substance can be detected because its spectrum contains a band at 1085 cm.$^{-1}$, due to the Si–O–Si grouping, which is intrinsically very strong. Because the methylsilyl amines, sulphides, or halides would be expected to be hydrolysed to form this ether [5, 8, 9] even by the minute quantities of water present in tap-grease, and since many of the compounds cannot be separated from it by fractional distillation, it was impossible to avoid slight contamination of this kind. The spectra of the halides and of dimethylsilane are illustrated in the Figures.

As mentioned above, much use has been made of vapour-phase band contours in the assignments that follow. Any vibration that produces a dipole change parallel to the axis of greatest moment of inertia should give rise to a band with type *C* contour (*P*, *Q*, and *R* branches with a particularly prominent *Q* branch). A dipole change parallel to the axis of intermediate moment of inertia should give a band of type *B* contour (a doublet *P*–*R* structure without the central *Q* branch), while a change parallel to the axis of least moment of inertia should give a band with contour of type *A* (*P*, *Q*, and *R* branches, often of comparable intensity).[10]

Assignments.—(1) *Dimethylsilane*, $CH_3{\cdot}SiH_2{\cdot}CH_3$. The molecule of dimethylsilane should have one two-fold rotational axis of symmetry, and two planes of symmetry perpendicular to that axis, corresponding to the symmetry group C_{2v}. Being an eleven-atomic molecule, it has 27 possible modes of vibration, but only 22 of them are infrared active. The vibrations, divided into their symmetry classes, are listed in Table 1.

Table 1. *Vibrations to be expected of the molecules of methylsilyl fluoride and dimethylsilane, with their symmetry classes and expected infrared band contours.*

	$CH_3{\cdot}SiH_2F$ Symmetry class		$CH_3{\cdot}SiH_2{\cdot}CH_3$ Symmetry class			
Vibration	A'	A''	A_1	A_2	B_1	B_2
Band contour	*A*–*B*	*C*	*B*	Forbidden	*A*	*C*
C–H stretch. (a)	ν_1	ν_{12}	ν_1	ν_{10}	ν_{15}	ν_{22}
C–H stretch. (s)	ν_2	—	ν_2	—	ν_{16}	—
Si–H stretch.	ν_3	ν_{13}	ν_3	—	—	ν_{23}
CH_3 deform. (a)	ν_4	ν_{14}	ν_4	ν_{11}	ν_{17}	ν_{24}
CH_3 deform. (s)	ν_5	—	ν_5	—	ν_{13}	—
SiH_2 bend. (scissors)	ν_6	—	ν_6	—	—	—
SiH_2 wag.	ν_7	—	—	—	ν_{19}	—
Si–F stretch.	ν_8	—	—	—	—	—
CH_3 rock.	ν_9	ν_{15}	ν_7	ν_{12}	ν_{20}	ν_{25}
Si–C stretch.	ν_{10}	—	ν_8	—	ν_{21}	—
SiH_2 twist.	—	ν_{16}	—	ν_{13}	—	—
SiH_2 rock.	—	ν_{17}	—	—	—	ν_{26}
C–Si–X deform.	ν_{11}	—	ν_9	—	—	—
CH_3 torsion	—	ν_{18}	—	ν_{14}	—	ν_{27}

The bonds from the silicon atom are probably directed tetrahedrally, making the C–Si–C bond angle greater than 90°. As the moment of inertia of the molecule as a whole must be largely governed by the relative positions of the heavy atoms, there can be little doubt that the axis of intermediate moment of inertia is parallel to the two-fold rotational axis, while the axis of least moment of inertia is perpendicular to the two-fold axis but lies in the plane of the heavy atoms. The axis of greatest moment of inertia is then perpendicular to this plane. It follows that vibrations of symmetry class A_1 will give bands with type *B* contours, those of class B_1

[5] Emeléus, Kuchen, and Onyszchuk, *Z. anorg. Chem.*, 1956, **283**, 74.
[6] Emeléus and Onyszchuk, unpublished work.
[7] Emeléus and Ebsworth, unpublished work.
[8] Emeléus, Macdiarmid, and Maddock, *J. Inorg. Nuclear Chem.*, 1955, **1**, 194.
[9] Sauer, *J. Amer. Chem. Soc.*, 1944, **66**, 1707.
[10] Badger and Zumwalt, *J. Chem. Phys.*, 1938, **6**, 711.

Fig. 2. ν = 1600—400 cm.$^{-1}$.

Fig. 1. ν = 4000—1500 cm.$^{-1}$.

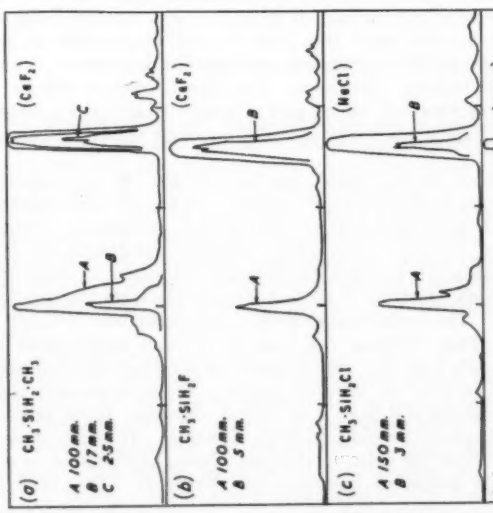

FIG. 1. ν = 4000—1500 cm.$^{-1}$.

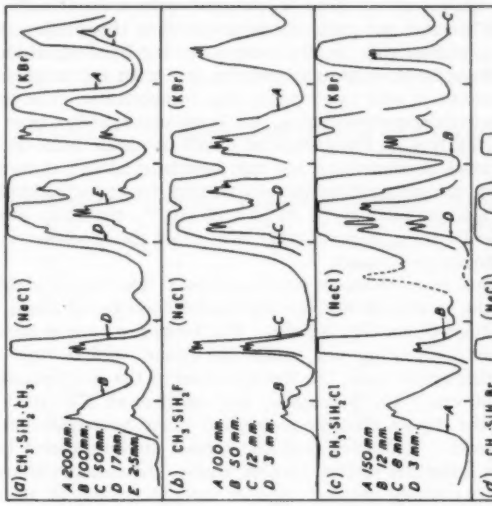

FIG. 2. ν = 1600—400 cm.$^{-1}$.

Vapour-phase infrared spectra of dimethylsilane and the methylsilyl halides, with the pressure at which each curve was recorded and the prism used (given in parentheses).

will give bands with type *A* contours, while those of class B_2 will give type *C* bands. In designating the B_1 and B_2 vibrations, the *x* axis is chosen to be in the plane of the heavy atoms, perpendicular to the two-fold (*z*) axis.[11]

In the spectrum recorded, the complex band at 2900—3000 cm.$^{-1}$ must include all the five active CH bond-stretching vibrations. Only one of these, ν_{22}, should give a band with a type *C* contour, and the sharp peak at 2970 cm.$^{-1}$ can probably be assigned to this mode; the remainder cannot be distinguished from one another. In the same way, the band at 2140—2150 cm.$^{-1}$ is due to both of the two SiH bond-stretching vibrations, but with the help of a calcium fluoride prism it is possible to resolve it into two overlapping components. The one at 2142 cm.$^{-1}$ has a type *C* contour, and so must correspond to ν_{23}, while the other, with a type *B* contour centred at about 2145 cm.$^{-1}$, is clearly ν_3. The groups of bands at about 1425 cm.$^{-1}$ and 1260 cm.$^{-1}$ are to be assigned to the three asymmetrical and two symmetrical CH_3 deformation frequencies respectively. The two symmetrical vibrations cannot be experimentally distinguished from one another and give a single band (type *A*) at 1260 cm.$^{-1}$; the sharp peak at 1430 cm.$^{-1}$ has been attributed specifically to ν_{24} because only this, of all the asymmetrical CH_3 deformation modes, should give rise to a type *C* band.

At frequencies below 1000 cm.$^{-1}$ the spectrum becomes more complex. The bands at 961 and 919 cm.$^{-1}$ do not have analogies in the spectra of fully methylated derivatives of silane,[12] and so must be due to deformation vibrations of the SiH_2 group. The former, a type *B* band, has been assigned to the bending (scissors) vibration (ν_6), while the latter, with a type *A* contour, may be identified with the wagging mode (ν_{19}). In the spectrum of the symmetrical-top molecule methylsilane, a band at 700 cm.$^{-1}$ has a parallel, and another at 873 cm.$^{-1}$ a perpendicular, contour,[13] showing that the dipole changes concerned must be parallel and perpendicular respectively to the C–Si bond. It follows that the former must represent the stretching vibration of that bond, and the latter the methyl rocking mode. In dimethylsilane, the two C–Si bond-stretching vibrations are directly coupled together through the silicon atom, and so may be expected to split into two separate bands with a mean frequency not very different from the value for the corresponding vibration in methylsilane. Hence the bands in the spectrum of dimethylsilane at 730 and 650 cm.$^{-1}$ almost certainly represent the two C–Si bond-stretching modes. Of the two, that at 730 cm.$^{-1}$ has a type *A* contour, and so is identified with the asymmetrical vibration (ν_{21}), while the other, with a less well-defined shape, is assigned to the symmetrical mode (ν_8). The methyl rocking vibrations in dimethylsilane are coupled together less directly than the bond-stretching modes, and so should lie in a smaller range of frequencies. The group of bands at 875—850 cm.$^{-1}$ lies close to the frequencies of the analogous vibrations of methylsilane [13] and of the more highly methylated derivatives,[12] and has therefore been assigned to the methyl rocking vibrations. The type *C* peak at 865 cm.$^{-1}$ is identified with the only one of these vibrations that should give a band with a type *C* contour (ν_{25}); the other two modes are probably hidden under the complex envelope centred at about 855 cm.$^{-1}$.

Since the SiH_2 twisting mode is forbidden, the only remaining band, at 467 cm.$^{-1}$, is assigned to the SiH_2 rocking mode (ν_{26}), in accordance with its *C* type contour. Of the 22 active modes, only the solitary active CH_3 torsional and the skeletal deformation vibrations remain unaccounted for. The former is likely to give very weak infrared absorption at low frequencies; [14] the frequency of the analogous skeletal deformation vibration of dimethyl sulphide appears at 278 cm.$^{-1}$ in the Raman spectrum,[15] so that its absence from the spectral range studied here is also to be expected. The overall assignments are summarised in Table 2.

(2) *Methylsilyl fluoride*, $CH_3{\cdot}SiH_2F$. This molecule can have at most a single plane of symmetry (symmetry group C_s) if the bonds from the silicon atom are directed tetrahedrally, so that all its 18 modes of vibration should be infrared active. Those occurring with a dipole change in the plane of the heavy atoms will have *A*–*B* hybrid contours; those producing a dipole change perpendicular to that plane should give type *C* bands. The assignments at frequencies higher than 1000 cm.$^{-1}$ follow the lines established above, although it is not possible to distinguish all the individual modes of vibration (see Table 2). The band at

[11] Herzberg, "Infra-red and Raman Spectra of Polyatomic Molecules," Van Nostrand, New York, 1945, pp. 359, 360.
[12] Tobin, *J. Amer. Chem. Soc.*, 1953, **75**, 1788.
[13] Randić and Sheppard, unpublished work.
[14] Sheppard and Simpson, *Quart. Rev.*, 1953, **7**, 19.
[15] Kohlrausch, "Ramanspektren," Becker and Erler, Leipzig, 1943.

975 cm.$^{-1}$ with a *B* type contour, and the type *A* band at 952 cm.$^{-1}$, have been assigned respectively to the bending and the wagging mode of the SiH_2 group by analogy with the bands of similar shape in the spectrum of dimethylsilane, for the moments of inertia of the two molecules will probably not differ greatly. Similarly, the C–Si bond-stretching vibration is identified with the absorption band at 760 cm.$^{-1}$. The group of bands at 850 cm.$^{-1}$ is more complex in this spectrum because, judging from the spectra of related compounds,[16, 17] the stretching frequency of the Si–F bond should appear in this region, in addition to the two CH_3 rocking modes. The type *C* contour that may be distinguished at 871 cm.$^{-1}$ is assigned to ν_{15}, the only

TABLE 2. *Analysis of the infrared spectra of methylsilyl fluoride and dimethylsilane.*

$CH_3{\cdot}SiH_2F$				$CH_3{\cdot}SiH_2{\cdot}CH_3$			
Frequency *	Strength	Contour	Vibration	Frequency *	Strength	Contour	Vibration
4225	w	—	$2\nu_3$	No data			
3130	w	—	$\nu_7 + \nu_3$	3060	w	—	$\nu_{19} + \nu_3$
2988	m	*C*	ν_{12}	2970	m	*C*	ν_{22}
2970	m	—	ν_1, ν_2	2980 to 2920	m —	—	$\nu_1, \nu_2,$ ν_{15}, ν_{16}
2910	w	—	—	2860	w	—	$\nu_4 + \nu_{17}$
~2185	s	*B*	ν_3	2145	s	*B*	ν_3
2185	s	*C*	ν_{13}	2142	s	*C*	ν_{23}
1945	w	—	$2\nu_6$	1912	w	—	$2\nu_6$
1910	w	—	$\nu_6 + \nu_7$				
1710	w	—	$2\nu_8$	1820	w	—	$2\nu_{10}$
1440	m	—	ν_4, ν_{14}	1430	m	*C*	ν_{24}
1418				1440 to 1380	m	—	ν_4, ν_{17}
1265	s	*A*	ν_5	1260	s	*A*	ν_5, ν_{18}
975	vs	*B*	ν_6	961	vs	*B*	ν_6
952	vs	*A*	ν_7	919	vs	*A*	ν_{19}
871	vs	*C*	ν_{15}	865	vs	*C*	ν_{25}
858	vs	*B*	ν_8				
850	vs	—	ν_9	855	s	—	ν_7, ν_{20}
760	s	—	ν_{10}	730	s	*A*	ν_{21}
733	s	*C*	ν_{16}				
				650	s	—	ν_8
522	m	*B*	$2\nu_{11}$				
510	m	*C*	ν_{17}	467	m	*C*	ν_{26}

* The spectra were recorded with a CaF_2 prism at frequencies higher than 2000 cm.$^{-1}$.

one of these vibrations that could give rise to such a band; the type *B* band at 858 cm.$^{-1}$ has been identified with the Si–F stretching frequency, while the remaining CH_3 rocking mode probably lies under the complex envelope at about 850 cm.$^{-1}$.

By analogy with dimethylsilane, the band at 510 cm.$^{-1}$ with a type *C* contour corresponds to the SiH_2 rocking mode (ν_{17}), while the overlapping type *B* band at 520 cm.$^{-1}$ probably represents the overtone of the skeletal deformation frequency ν_{11} (the frequency seems to be too high to be that of the fundamental). There remains a strong band with a type *C* contour at 733 cm.$^{-1}$, which must be identified with the SiH_2 twisting mode (ν_{16}). Of the 18 possible vibrations, only the torsional oscillation of the methyl group remains unaccounted for in this case.

(3) *Compounds* $CH_3{\cdot}SiH_2X$, *where* X = Cl, Br, I, *or* NC. Apart from variations in skeletal frequencies, the spectra of these compounds are very like that of methylsilyl fluoride. The band due to the SiCl bond-stretching vibration appears at 527 cm.$^{-1}$ in the spectrum of the chloride, and the SiBr stretching mode at ~415 cm.$^{-1}$ in the bromide's spectrum. The spectrum of the *iso*cyanide was not recorded in the range 650—400 cm.$^{-1}$; the Si–I frequency was not observed but would be expected to lie outside the range covered by the potassium bromide prism, as the corresponding frequencies of silyl [18] and trimethylsilyl iodide [19] are at ~355 and 331 cm.$^{-1}$, respectively. Otherwise, the spectra can easily be correlated with one another.

[16] Newman, O'Loane, Polo, and Wilson, *J. Chem. Phys.*, 1956, **25**, 855.
[17] Ebsworth, Onyszchuk, and Sheppard, unpublished work.
[18] Dixon and Sheppard, *Trans. Faraday Soc.*, 1957, **53**, 282.
[19] Goubeau and Sommer, *Z. anorg. Chem.*, 1957, **289**, 1.

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The frequency of the SiH_2 twisting mode decreases considerably in the series X = F to X = I, as does its intensity. The frequency of the wagging vibration also drops in the same way, making it progressively harder to distinguish the bands due to the rocking of the methyl group. The various assignments are summarised in Table 3. The stretching frequency of the NC bond was not observed, but is probably overlaid by the strong ν_{Si-H} absorption band; [17] in methyl *iso*cyanide [16] the corresponding ν_{NC} frequency is 2161 cm.$^{-1}$.

(4) *Di(methylsilyl) ether,* $(CH_3{\cdot}SiH_2)_2O$, *di(methylsilyl) sulphide,* $(CH_3{\cdot}SiH_2)_2S$, *and tri(methylsilyl)amine,* $(CH_3{\cdot}SiH_2)_3N$. The spectra of these compounds are in principle too complicated for detailed analysis; but by assuming that the methylsilyl groups vibrate relatively independently it is possible to pick out the bands due to certain groups of vibrations by using the assignments described above for the simpler spectra. Very satisfactory correlations result from this procedure (see Table 3).

The spectra of both the amine and the ether should contain at least one band in the frequency

TABLE 3. *Assignments of the bands observed in the spectra of molecules of the type* $(CH_3{\cdot}SiH_2)_nX$.

	$CH_3{\cdot}SiH_2F$	$CH_3{\cdot}SiH_2Cl$	$CH_3{\cdot}SiH_2Br$	$CH_3{\cdot}SiH_2I$	$CH_3{\cdot}SiH_2{\cdot}NC$
C–H stretch.	2988, 2970 *	2985, 2930	2985, 2915	2985, 2874	2967
Si–H stretch.	2185 *	2200	2198	2190	2198
CH_3 deform. (as)	1440, 1418	1442, 1410	1425	1418	1422
CH_3 deform. (s)	1265	1265	1265	1264	1266
SiH_2 bend. (scissors)	975	960	955	947	948
SiH_2 wag.	952	912	898	880	900
CH_3 rock.	871 (*C*) 850	873 ?900	870 ?922	~855 —	877 —
Si–C stretch.	760	751	740	735	758
SiH_2 twist.	733 (*C*)	682	656	?631	707 (*C*)
SiH_2 rock.	510	~510	495	480	No data
Si–X stretch.	858	527	~415	—	—
C–Si–X deform.	(261)	—	—	—	—

	$(CH_3)_2SiH_2$	$(CH_3{\cdot}SiH_2)_2O$	$(CH_3{\cdot}SiH_2)_3N$	$(CH_3{\cdot}SiH_2)_2S$
C–H stretch.	~2970 *	2970, 2920 *	2967, 2907	2970
Si–H stretch.	2145 *	2158 *	2146	2160
CH_3 deform. (as)	1440, 1380	1418, 1375	1453, 1418, 1380	1375
CH_3 deform. (s)	1260	1264	1260	1260
SiH_2 bend. (scissors)	961	964	955	952 †
SiH_2 wag.	919	915	907	878
CH_3 rock.	865	880	~880	?
Si–C stretch.	730, 650	763	765	740
SiH_2 twist.	Forbidden	?670	723	?
SiH_2 rock.	467	520	510	No data
Si–X stretch.	—	1085	987	—
C–Si–X deform.	—	—	—	—

* Recorded by using a CaF_2 prism. † There is another band at 913 cm.$^{-1}$ in the spectrum of the sulphide.

range studied due to one of the Si–X bond-stretching vibrations. There is a strong band at 1085 cm.$^{-1}$ in the ether's spectrum that cannot be assigned to any other group.

In the spectrum of the amine, once the bands characteristic of the methylsilyl groups have been identified, there remains a strong band at 987 cm.$^{-1}$ which has therefore been assigned to the asymmetrical Si–N bond-stretching mode.

DISCUSSION

In all the spectra described above, the stretching vibrations of the CH, SiH, and SiC bonds and the deformation modes of the CH_3 group appear at frequencies close to those observed in the spectra of other compounds which contain these groups. The SiF bond-stretching mode in $CH_3{\cdot}SiH_2F$ has been assigned to a band at a frequency (858 cm.$^{-1}$) similar to those of the corresponding vibrations in the spectra of silyl fluoride [16] (872 cm.$^{-1}$) and of trimethylsilyl fluoride [17] (916 cm.$^{-1}$). The SiCl and SiBr bond-stretching frequencies (527 cm.$^{-1}$, ~415 cm.$^{-1}$) and the band assigned to the asymmetric Si–O–Si bond-stretching

vibration (1087 cm.$^{-1}$) are also close to the frequencies reported for the analogous vibrations in the spectra of the corresponding silyl derivatives [551 cm.$^{-1}$ (refs. 16, 20), 430 cm.$^{-1}$, (ref. 16) and 1107 cm.$^{-1}$ (ref. 21), respectively]. Only one band that could be assigned to a Si–N bond-stretching mode was observed in the spectrum of tri(methylsilyl)amine (987 cm.$^{-1}$); this may be significant in view of Hedberg's conclusion [22] from electron-diffraction studies that the silicon and nitrogen atoms in the molecule of trisilylamine are coplanar. If this were also true of tri(methylsilyl)amine (the two amines are chemically very much alike [7]), the symmetrical Si–N stretching vibration ought to be forbidden or very weak in the infrared spectrum, depending on the overall configuration of the molecule.

TABLE 4. SiH_2 *Deformation frequencies in the molecules* $(CH_3)_2SiH_2$, $CH_3{\cdot}SiH_2X$, *and* SiH_2X_2, *where* X *is* F, Cl, Br, *or* I.

Vibration	SiH_3F_3 [17]	$CH_3{\cdot}SiH_2F$	$(CH_3)_2SiH_2$	$CH_3{\cdot}SiH_2Cl$	SiH_2Cl_2 [24]
Bending	985	975	961	960	953
Wagging	?~975	952	919	912	877
Twisting	—	733	—	682	710
Rocking	?	510	467	~510	610
	SiH_2Br_2 [25, 26]	$CH_3{\cdot}SiH_2Br$	$(CH_3)_2SiH_2$	$CH_3{\cdot}SiH_2I$	SiH_2I_2 [8, 17]
Bending	942	955	961	947	925
Wagging	843	898	919	880	791
Twisting	688 *	656	—	631	—
Rocking	556	495	467	480	497 †

* Raman data. † In the infrared spectrum of the liquid.

The frequencies of the four SiH_2 deformation modes are now clearly established in the spectra of several compounds of formula $CH_3{\cdot}SiH_2X$, and it is interesting to see how they change as the atom X is varied. The frequencies might be influenced either by the mass of X, or by electronic effects connected with that atom's electronegativity—in other words, through induced changes in the force-constants of the bonds concerned. The frequencies of the bending and of the wagging modes have been plotted against the electronegativity of the atom X, and the points in each case lie very close to a straight line. This has previously been shown to be true of one of the CH_3 deformation frequencies.[23] The observation that the values for the bending and wagging modes from the spectra of di(methylsilyl) ether and tri(methylsilyl)amine fall on the appropriate lines shows clearly that the electronegativity of X is the operative factor here, for nitrogen and chlorine have the same electronegativity but probably differ considerably in reduced mass. This relation between the frequencies of the bending and wagging modes and electronegativity influenced the choice made when one of two bands had to be assigned to the SiH_2 wagging vibration in the spectrum of di(methylsilyl) sulphide. The twisting and rocking frequencies do not vary with electronegativity in the same simple fashion.

It is also interesting to compare the deformation frequencies of the SiH_2 group observed in the spectra of the methylsilyl halides with those recorded for dimethylsilane and the silylene halides (see Table 4). The spectra of silylene chloride and bromide had been analysed in detail,[24, 25, 26] and the frequencies obtained in the present work fit in well with these.

Westermark,[4] following West and Rochow,[1] found that in the spectra of a number of more complex dialkylsilanes there were three characteristic absorption bands between

[20] Monfils, *Mem. Acad. roy. Belg.* (*Classe des Sciences*), 1956, **29**, 7.
[21] Lord, Robinson, and Schumb, *J. Amer. Chem. Soc.*, 1956, **78**, 1327.
[22] Hedberg, *ibid.*, 1955, **77**, 6491.
[23] Sheppard, *Trans. Faraday Soc.*, 1955, **51**, 1465.
[24] Hawkins and Wilson, *J. Chem. Phys.*, 1953, **21**, 360.
[25] Hawkins, Polo, and Wilson, *ibid.*, p. 1122.
[26] Mayo, Opitz, and Peake, *ibid.*, 1955, **23**, 1344.

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660 and 1000 cm.$^{-1}$. The strongest was at about 940 cm.$^{-1}$, while others appeared at about 890 and 715 cm.$^{-1}$. On the basis of the assignments made above for dimethylsilane, it seems reasonable to associate the first of these bands with the SiH_2 bending and the second with the SiH_2 wagging modes, while the last band is probably due to one of the Si–C stretching vibrations. The analogous frequencies in the spectrum of the dimethyl compound (see above) are 961, 919, and 730 cm.$^{-1}$, respectively. Similarly, the bands in the spectra of dialkylsilanes at 938—917 and 862—826 cm.$^{-1}$ which Opitz *et al.*[3] have assigned to a deformation and a rocking mode of the SiH_2 group, respectively, are more accurately to be described as representing the bending and the wagging modes.

We are grateful to King's College, Cambridge, for a Harold Fry Studentship, and to the Department of Scientific and Industrial Research for a maintenance grant (to E. A. V. E.), and to the Royal Commission for the Exhibition of 1851 for an Overseas Scholarship (to M. O.).

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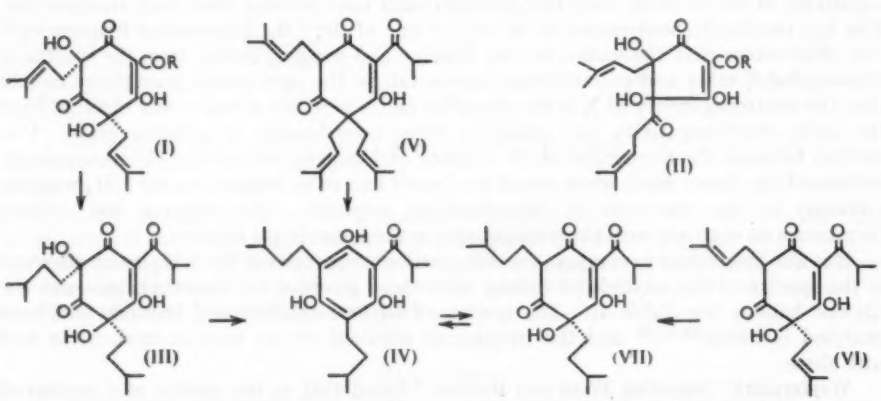
292. *The Chemistry of Hop Constituents. Part XII.* The Structure of Humulinone.*

By G. A. HOWARD and C. A. SLATER.

Structures of type (I) are proved for humulinone and its analogues.

IT was earlier suggested [1] that humulinone and its analogues had the general structure (I) rather than the alternative (II) involving a five-membered ring. More recently, on the other hand, the latter was preferred by Alderweireldt and Verzele,[2] primarily because of the low pK value and the infrared absorption of the compound. The present paper presents chemical evidence which proves the original structure (I).

Cohumulinone, which differs from humulinone only in the nature of its acyl side-chain,[1]



was hydrogenated to tetrahydrocohumulinone (III), the only structural change being the saturation of the double bonds of the two alkyl side-chains. The same compound was also obtained by the oxidation, by cumenyl hydroperoxide, of tetrahydrocohumulone (VII)

* Part XI, *J. Inst. Brewing*, 1957, 327.

[1] Cook, Howard, and Slater, *J. Inst. Brewing*, 1955, 321.
[2] Alderweireldt and Verzele, *Bull. Soc. Chim. belges*, 1957, **66**, 391.

itself derived from cohumulone (VI). Clemmensen reduction of the compound gave a phenol characterised as its tribenzoate, together with a hydrocarbon, $C_{20}H_{40}$. The phenolic product was also obtained by hydrogenolysis of colupulone [3] (V) and was oxidised to tetrahydrocohumulone (VII) by air in the presence of lead acetate.[3] No doubt is attached to the presence of six-membered rings [3,4] in compounds (V) and (VI), so that the new phenolic product must be 2 : 4 : 6-trihydroxy-3 : 5-di*iso*pentyl*iso*butyrophenone (IV). It follows that cohumulinone must likewise contain a six-membered ring and be regarded as (I; R = Pr^i), the analogous compounds humulinone and adhumulinone [5] being as (I; R = Bu^i) and (I; Bu^s) respectively.

Neither humulinone nor cohumulinone is optically active when derived respectively, from the natural optically active humulone or cohumulone, presumably because the oxidation is so directed as to give internally compensated compounds.[1] Adhumulone differs from the analogues already mentioned in containing a further asymmetric carbon atom in the acyl side-chain. Adhumulinone derived from natural adhumulone might be expected therefore to differ from that obtained from synthetic (racemic) adhumulone. This has now been proved to be the case as " natural " adhumulinone prepared in these laboratories had m. p. 114—115° and $[\alpha]_D$ +11° " Synthetic " adhumulinone had m. p. 98°, α 0°.

Experimental

Tetrahydrocohumulinone (III).—(*a*) A solution of tetrahydrocohumulone [3] (3·1 g.) in ether (10 ml.) containing cumenyl hydroperoxide (3·1 ml.) was kept over saturated aqueous sodium hydrogen carbonate (50 ml.) for 3 days. The colourless sodium salt (2·75 g., 81%) was filtered off and afforded in the usual manner *tetrahydrocohumulinone*, m. p. 64—65°, which could not be recrystallised (Found: C, 65·1; H, 8·8. $C_{20}H_{32}O_6$ requires C, 65·2; H, 8·7%). It had $\lambda_{max.}$ 230 and 270 mμ (ε 9160 and 10,200 respectively) in acidic ethanol and $\lambda_{max.}$ 255 and 270 (infl.) mμ (ε 22,500 and 20,400 respectively) in alkaline ethanol. The compound was bitter, gave an orange-red colour with methanolic ferric chloride and a yellow colour with concentrated sulphuric acid and, like tetrahydrocohumulone, failed to reduce Fehling's solution.

(*b*) Cohumulinone (344 mg.) was hydrogenated overnight in acetic acid over Adams platinum oxide. The solution was filtered, the filtrate evaporated *in vacuo*, and the residue shaken with ether and saturated aqueous sodium hydrogen carbonate. The sodium salt thus formed afforded tetrahydrocohumulinone as colourless needles, m. p. 62—64° undepressed on admixture with the compound prepared from tetrahydrocohumulone.

Clemmensen Reduction of Tetrahydrocohumulone.—A solution of tetrahydrocohumulone (0·68 g.) in ethanol (5 ml.) was boiled with amalgamated zinc (20 g.) in concentrated hydrochloric acid (12 ml.) for 1·75 hr. The product was extracted by light petroleum and the extract kept overnight in pyridine (5 ml.) containing benzoyl chloride (0·78 g.). The product isolated in the usual way crystallised from methanol as colourless prisms (0·14 g.), m. p. 137—138°, undepressed on admixture with 2 : 4 : 6-tribenzoyloxy-3 : 5-di*iso*pentyl*iso*butyrophenone prepared from colupulone.[3]

Clemmensen Reduction of Tetrahydrocohumulinone.—A solution of tetrahydrocohumulinone (0·38 g.) in ethanol (5 ml.) was heated with amalgamated zinc (20 g.) and concentrated hydrochloric acid (12 ml.) for 4·75 hr. The product was isolated and the crude benzoylation product chromatographed on alumina. The fraction eluted by 4 : 1 light petroleum–ether recrystallised from methanol, giving prisms (20 mg.), m. p. 136—137° undepressed on admixture with the preceding tribenzoate. The fraction eluted from the chromatogram by light petroleum was rechromatographed on silica gel (from Messrs. Hopkin and Williams). The *substance* (75 mg.) eluted by light petroleum had b. p. 110—115° (bath)/6 × 10^{-4} mm., n_D^{25} 1·4600 (Found: C, 86·1; H, 13·9. $C_{20}H_{40}$ requires C, 85·7; H, 14·3%).

Adhumulinone from Natural Adhumulone.—A solution of the (−)-adhumulone (0·75 g.), isolated from hops,[6] in ether (3 ml.) containing cumenyl hydroperoxide (0·7 ml.) was kept over

[3] Howard, Pollock, and Tatchell, *J.*, 1955, 174.
[4] Howard, *Chem. and Ind.*, 1956, 1504.
[5] Cook, Howard, and Slater, *J. Inst. Brewing*, 1956, 220.
[6] Rigby and Bethune, *J. Amer. Chem. Soc.*, 1955, **77**, 2828.

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saturated aqueous sodium hydrogen carbonate (10 ml.) for 7 days. The sodium salt (0·52 g., 63%) was filtered off and the free acid recrystallised from light petroleum (b. p. 60—80°), as needles, m. p. 114—115° (Found: C, 66·7; H, 8·1. Calc. for $C_{21}H_{30}O_4$: C, 66·6; H, 7·9%). On admixture with adhumulinone from synthetic adhumulone it had m. p. 102—109°. It had $[\alpha]_D$ + 11° (*c* 5·36 in MeOH), tasted bitter, gave an orange colour with methanolic ferric chloride and a cherry-red colour with concentrated sulphuric acid and rapidly reduced Fehling's solution.

The authors thank F. L. Rigby and J. L. Bethune for a gift of natural adhumulone.

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[*Received, November 7th*, 1957.]

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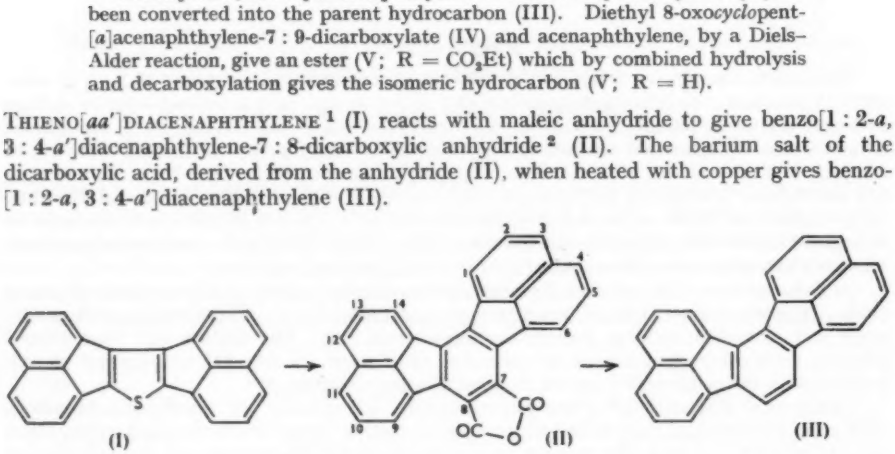
293. *Synthesis of Fluoranthenes. Part XIII.* Synthesis of Benzo*[1 : 2-a, 3 : 4-a′]- *and of Benzo*[1 : 2-a, 4 : 5-a′]-*diacenaphthylene.*

By S. HORWOOD TUCKER.

Benzo[1 : 2-*a*, 3 : 4-*a*′]diacenaphthylene-7 : 8-dicarboxylic anhydride (II) has been converted into the parent hydrocarbon (III). Diethyl 8-oxo*cyclo*pent-[*a*]acenaphthylene-7 : 9-dicarboxylate (IV) and acenaphthylene, by a Diels–Alder reaction, give an ester (V; R = CO_2Et) which by combined hydrolysis and decarboxylation gives the isomeric hydrocarbon (V; R = H).

THIENO[*aa*′]DIACENAPHTHYLENE [1] (I) reacts with maleic anhydride to give benzo[1 : 2-*a*, 3 : 4-*a*′]diacenaphthylene-7 : 8-dicarboxylic anhydride [2] (II). The barium salt of the dicarboxylic acid, derived from the anhydride (II), when heated with copper gives benzo-[1 : 2-*a*, 3 : 4-*a*′]diacenaphthylene (III).



The isomeric benzo[1 : 2-*a*, 4 : 5-*a*′]diacenaphthylene (V; R = H) was synthesised as follows. Condensation of acenaphthenequinone with diethyl acetonedicarboxylate [3] gives diethyl 8-oxo*cyclo*pent[*a*]acenaphthylene-7 : 9-dicarboxylate [4] (IV). When this diester (IV) and acenaphthylene are heated together at *ca.* 250°, carbon monoxide and hydrogen are removed, and diethyl benzo[1 : 2-*a*, 4 : 5-*a*′]diacenaphthylene-7 : 14-dicarboxylate (V; R = CO_2Et) is formed. This diester is hydrolysed and decarboxylated in one step

* Part XII, *J.*, 1954, 227.

[1] Dziewonski, *Ber.*, 1903, **36**, 962.
[2] Clapp, *J. Amer. Chem. Soc.*, 1939, **61**, 2733.
[3] Cf. Dilthey, ter Horst, and Schommer, *J. prakt. Chem.*, 1935, **143**, 208.
[4] Allen and VanAllan, *J. Org. Chem.*, 1952, **17**, 845.

by heating it with 100% phosphoric acid:[5] benzo[1 : 2-*a*, 4 : 5-*a'*]diacenaphthylene (V; R = H) is produced. The intermediate dihydro-derivative of (V; R = H) has also been isolated.

An attempt was made to synthesise the hydrocarbon (V; R = H) by the general method of Forrest and Tucker.[6] 1-Iodonaphthalene was heated with 1 : 5-dibromo-2 : 4-dinitrobenzene [7] in presence of copper, to give 1 : 5-di-(1-naphthyl)-2 : 4-dinitrobenzene, but the yield varied uncontrollably. Reduction by several methods gave no crystallisable diamine. Accordingly, the red oil obtained on reduction was diazotised at once. A very small amount of impure hydrocarbon (V; R = H) resulted.

Separation of *cis*- and *trans*-1 : 2-dimethylacenaphthene-1 : 2-diol has been improved,[8] but both the *cis*- and the *trans*-isomer, treated with acenaphthylene under a variety of conditions,[9] failed to give an isolable addition product.

Experimental

Synthesis of Benzo[1 : 2-a, 3 : 4-a']*diacenaphthylene* (III).—Thieno[*aa'*]diacenaphthylene (II) (crystallised from dioxan), when treated with maleic anhydride,[2] gave benzo[1 : 2-*a*, 3 : 4-*a'*]-diacenaphthylene-7 : 8-dicarboxylic anhydride (II). The barium salt prepared from this, when heated with copper,[10] gave a yellow sublimate, which, with excess of picric acid in acetone, formed rectangular magenta-coloured laths of a *picrate*, m. p. 239—240°, with slight shrinkage at 120° (Found: C, 69·0; H, 3·3; N, 7·8. $C_{26}H_{14},C_6H_3O_7N_3$ requires C, 69·2; H, 3·1; N, 7·6%). Chromatography of this picrate on alumina in benzene, and crystallisation from benzene–ethanol, then from ethyl acetate, yielded canary-yellow needles of *benzo*[1 : 2-a, 3 : 4-a']*diacenaphthylene* (III), m. p. 232—233°, softening at 227° (Found: C, 95·6; H, 4·3. $C_{26}H_{14}$ requires C, 95·7; H, 4·3%). Its solutions fluoresce green. Its ultraviolet absorption spectrum in ethanol shows $\lambda_{max.}$ (log ε in parentheses) 352 (4·74), 336 (4·60), 281 (4·15), 270 (4·18), 242 mμ (4·68).

Synthesis of Benzo[1 : 2-a, 4 : 5-a']*diacenaphthylene* (V; R = H).—*Diethyl 8-oxocyclopent*[a]*acenaphthylene-7 : 9-dicarboxylate* (IV). Acenaphthenequinone (crystallised from dioxan; m. p. 252°; lit., 261°; 0·91 g.), diethyl acetonedicarboxylate (1·01 g.), methanol (10 ml.), and redistilled triethylamine (1·0 ml.) in methanol (5 ml.) were mixed at room temperature. The quinone gradually dissolved to give a brown solution, with evolution of heat. In 30 min. the solution was purple. The purple needles which separated crystallised from acetic anhydride to give the ester (IV) which, heated rapidly, had m. p. 189—191° (lit.,[4] m. p. 196°) (0·86 g., 50%). When, instead of triethylamine, the recommended [3,4] potassium hydroxide in aqueous methanol was used results were unreliable.

Diethyl benzo[1 : 2-a, 4 : 5-a']*diacenaphthylene-7 : 14-dicarboxylate* (V; R = CO_2Et). The ester (IV) (0·35 g., 1 mol.) and acenaphthylene (0·32 g., >2 mol.) were heated at 125° until carbon monoxide evolution ceased (1 min.). The product was heated at the same temperature with chloranil (0·25 g., 1 mol.) for 5 min. The black melt dissolved completely in xylene, and the solution on storage gave green-yellow crystals. These were boiled with benzene. The insoluble residue (0·39 g.), with material recovered by adding the benzene extracts to the xylene liquors, was recrystallised from dioxan or nitromethane to give orange-yellow thick square plates (0·44 g., 93%), m. p. 310—312°, softening at 307°, of *ester* (V; R = CO_2Et) (Found: C, 81·6; H, 4·9. $C_{32}H_{22}O_4$ requires C, 81·7; H, 4·7%). Its solutions are orange-yellow with a deep green fluorescence.

When the above mixture, but with chloranil omitted, was heated at 230—250° for 4 hr., the product was almost entirely the above compound.

Diethyl 6b : 14a-Dihydrobenzo[1 : 2-a, 4 : 5-a']*diacenaphthylene-7 : 14-dicarboxylate*.—This

[5] Cf. Orchin and Regel, *J. Amer. Chem. Soc.*, 1951, **73**, 436; Berger and Olivier, *Rec. Trav. chim.*, 1927, **46**, 600; Moureu, Chovin, and Rivoal, *Bull. Soc. chim. France*, 1946, **13**, 106; 1948, **15**, 99.
[6] Forrest and Tucker, *J.*, 1948, 1137.
[7] Hodgson, *J. Soc. Dyers and Colourists*, 1926, **42**, 367.
[8] Criegee, Kraft, and Rank, *Annalen*, 1933, **507**, 177; Maxim, *Bull. Soc. chim. France*, 1928, **43**, 769; 1929, **45**, 1137.
[9] Cf. Campbell, Gow, and Wang, *Nature*, 1948, **162**, 857; Campbell and Gow, *J.*, 1949, 1555.
[10] Cf. Szmuszkovicz and Modest, *J. Amer. Chem. Soc.*, 1950, **72**, 577.

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compound was isolated after a benzene solution (3 ml.) of diethyl 8-oxo*cyclo*pent[*a*]acenaphthylene-7 : 9-dicarboxylate (0·17 g.) and acenaphthylene (0·08 g.) had been boiled for 2 hr. On cooling, crystals separated and gave, from acetone, pale green hexagonal-sided thick plates of the *dihydro-compound*, m. p. 210—212° (0·16 g., 68%) (Found: C, 81·6; H, 4·9. $C_{32}H_{24}O_4$ requires C, 81·3; H, 5·1%).

Hydrolysis of the ester (V; R = CO_2Et). The ester (0·14 g.) was boiled in 2-ethoxyethanol (5 ml.) solution with 50% potassium hydroxide solution (2 ml.) for 4 hr. The solution was acidified, then filtered through charcoal to remove the precipitated dicarboxylic acid and silica (filtration was slow). The washed residue was extracted with aqueous ammonia, excess of ammonia removed by boiling, and glacial acetic acid added. The green-yellow precipitate was satisfactorily filtered off under slightly reduced pressure. It crystallised in pale yellow blades from acetic anhydride, was washed with acetic acid, and dried in air overnight. It sintered at 300° but was unmelted at 350°. The solvated *acid* (V; R = CO_2H) so isolated may not be pure (Found: C, 75·6; H, 3·85. $C_{28}H_{14}O_4,C_2H_4O_2$ requires C, 75·9; H, 3·8%). Crystallisation from propionic anhydride gave crystals of uncertain composition.

It was therefore considered preferable to hydrolyse and decarboxylate the ester in one operation by means of 100% phosphoric acid.[5]

Hydrolysis in 2-methoxyethanol gave similar results, but the product in this experiment was crystallised from pyridine, with production of short orange blade-prisms, unmelted at 350°, which consisted of *dipyridinium benzo*[1 : 2-a, 4 : 5-a′]*diacenaphthylene*-7 : 14-*dicarboxylate* (Found: C, 79·9; H, 4·3; N, 4·8. $C_{28}H_{14}O_4,2C_5H_5N$ requires C, 79·7; H, 4·2; N, 4·9%.)

Benzo[1 : 2-a, 4 : 5-a′]*diacenaphthylene* (V; R = H). The ester (V; R = CO_2Et) (0·56 g.) was heated with 100% phosphoric acid (10 ml.) in the vapour of boiling dimethyl phthalate (b. p. 282°; thermometer in vapour registered 275°) for 1 hr. whilst stirred with a copper-wire stirrer. The black-green solid was extracted thoroughly with benzene, and the extract chromatographed on alumina. The clear golden-yellow eluate was concentrated and gave golden-yellow needles, changing to yellow at 290°, but melting sharply at 315°, of *benzo*[1 : 2-a, 4 : 5-a′]-*diacenaphthylene* (Found: C, 95·5; H, 4·3. $C_{26}H_{14}$ requires C, 95·7; H, 4·3%). The filtrate deposited also short rod-prisms which were pale yellow and showed a bright green fluorescence when crushed. There was insufficient for further examination.

Attempted Synthesis of Benzo[1 : 2-a, 4 : 5-a′]*diacenaphthylene* (V; R = H).—1 : 5-*Di*-(1-*naphthyl*)-2 : 4-*dinitrobenzene*. 1-Iodonaphthalene (3·81 g., 0·015 mol.), 1 : 5-dibromo-2 : 4-dinitrobenzene [7] (1·63 g., 0·005 mol.), and copper bronze (3 g.) were heated together at 244° (diethylene glycol vapour) for 2·5 hr., and the product extracted with benzene. The concentrated solution was chromatographed on alumina. The first small amount of eluate, fluorescing blue in ultraviolet light, was discarded. The following yellow eluate (150 ml.) on evaporation gave a red oil: this was dissolved in acetic acid and treated with an equal volume of ethanol. The liquid became turbid, and when boiled suddenly gave orange crystals: these recrystallised from carbon tetrachloride to give 1 : 5-*di*-(1-*naphthyl*)-2 : 4-*dinitrobenzene*, m. p. 212—213°, (0·84 g., 40%) (Found: C, 74·4; H, 3·9; N, 6·9. $C_{26}H_{16}O_4N_2$ requires C, 74·3; H, 3·8; N, 6·7%).

This procedure was unreliable, especially on a larger scale. Heating the above mixture at 282° (dimethyl phthalate) or at its b. p. (305°) for 30 min. gave the same capricious results. Clean yellow products were obtained but they did not always crystallise.

Reduction of the above dinitro-compound with hydrogen and Raney nickel in suspension in ethanol alone, or in solution in benzene and ethanol, gave no crystallisable product. Reduction by stannous chloride in glacial acetic acid saturated with dry hydrogen chloride gave in the usual way an oil: this was diazotised and then heated on the boiling-water bath. A brick-red solid was obtained. Its chromatographed (alumina) benzene solution gave a canary-yellow eluate with a deep green fluorescence, and a yellow solid was isolated: it crystallised in needles, from dioxan, softening at 290°, m. p. 300—310°. It appears to be crude benzo-[1 : 2-*a*, 4 : 5-*a*′]diacenaphthylene (V; R = H).

The crude diamine gave a green-yellow *picrate* in, and crystallised from, benzene; the crude product contained benzene of crystallisation which was lost at 80° (Found: C, 60·4; H, 3·5; N, 11·9. $C_{26}H_{20}N_2,2C_6H_3O_7N_3,2C_6H_6$ requires C, 61·6; H, 3·9; N, 11·5%).

cis- *and* trans-1 : 2-*Dimethylacenaphthene*-1 : 2-*diol*.[8]—Acenaphthenequinone was treated with methylmagnesium iodide in ether, and the solution with aqueous ammonium chloride (not mineral acid), in the usual way. The crude mixture of *cis*- and *trans*-diols (13·0 g.) was

separated by crystallisation from acetone, giving thick square plates of *cis*-diol, m. p. 187—189° (3·13 g., 24%). When, during the crystallisation, needles began to separate with the plates, the filtrate was evaporated to dryness, and the residue crystallised from chloroform, to give *trans*-isomer, m. p. 182—183° (4·60 g., 35%). The *cis*-isomer is only slightly soluble in chloroform. Each isomer was heated with acenaphthylene in acetic anhydride, phthalic anhydride, and a trace of toluene-*p*-sulphonic acid,[11] and in phosphoric acid. No addition product could be isolated. The diol, acenaphthylene, chloranil, and a crystal of iodine were heated at 190°. Water was evolved. Chromatography in benzene on alumina gave an orange-fluorescent column (ultraviolet light) and eventually a red oil, which after treatment became solid, and melted at 180—220°.

I thank Dr. K. F. Lang, Rütgerswerke-Aktiengesellschaft, Frankfurt am Main, for a gift of thieno[*aa*']diacenaphthylene. Microanalyses were performed by Miss A. McMillan.

THE UNIVERSITY, GLASGOW. [*Received, November 26th*, 1957.]

[11] Cf. Waldmann and Petrů, *Chem. Ber.*, 1950, **83**, 287; Waldmann and Schubert, *ibid.*, 1951, **84**, 139.

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294. *Molecular Polarisability. The Anisotropies of Seven Monosubstituted Benzenes and of Nitromethane as Solutes in Carbon Tetrachloride.*

By R. J. W. LE FÈVRE and B. PURNACHANDRA RAO.

The molecular anisotropies at infinite dilution in carbon tetrachloride of $CH_3{\cdot}NO_2$ and C_6H_5X (with X = CH_3, F, Cl, Br, I, NO_2, and CN) have been determined, by measurements of the depolarisation factors of light scattered by solutions, and these data, in combination with molecular refractions and Kerr constants previously recorded, are used to calculate the semi-axes of the polarisability ellipsoids of these molecules. Such semi-axes are entirely based upon experiment and are free from certain assumptions made formerly; the indications they provide regarding the directed exaltations of polarisability in the Ar-structures are summarised in Table 5(*B*).

LE FÈVRE and LE FÈVRE,[1,2] when computing semi-axes for the molecular polarisability ellipsoids of a number of monosubstituted benzenes, were handicapped in two respects: (*a*) by scattered light-depolarisation factors being available only for toluene and chloro-, bromo-, and nitro-benzene, and (*b*) by the absence of evidence showing whether or not depolarisation data for gaseous substances were appropriate for use in conjunction with molar Kerr constants and refractions determined from observations on solutions. Consequently, certain of the polarisabilities listed then and since (*e.g.*, in Table 4 of ref. 1, or Table 9 of ref. 2) have been perforce derived by methods which involved empirical assumptions concerning the smallest of the three semi-axes in each case. The problem mentioned in (*b*) above, however, has recently been solved by measurements by Le Fèvre and Rao,[3] which indicate depolarisation factors of *solutions* as the correct source in the circumstances stated. There thus occurs an opportunity to check or amend earlier results.

Present Work.—Accordingly, the molecular anisotropies at infinite dilution, ${}_\infty\delta_2^2$, of toluene, the four halogenobenzenes, nitrobenzene, and benzonitrile, have been determined in carbon tetrachloride; also that for nitromethane has been ascertained, since this datum was needed but was lacking when our earlier papers [1,2] were prepared.

Experimental methods, symbols, and calculation procedures have been explained before.[3] All materials were redistilled, dry specimens; solvent and solutions were made

[1] Le Fèvre and Le Fèvre, *J.*, 1954, 1577.
[2] Le Fèvre and Le Fèvre, *Rev. Pure Appl. Chem.*, 1955, **5**, 261.
[3] Le Fèvre and Rao, *J.*, 1957, 3644.

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equally dust-free as described before;[3] with iodobenzene it was found necessary to remove traces of free iodine by passage through an alumina-packed column immediately before use, otherwise a general scattering prevented accurate readings. Essential observations are recorded in Tables 1 and 2; densities of mixtures are not included since in all cases these are available from published dielectric polarisation measurements.[4]

TABLE 1. *Depolarisation factors for solutions in carbon tetrachloride.**

	Solute: toluene					*Solute: fluorobenzene*				
$10^5 f_2$	3759	10,776	15,986	21,039	22,503	2944	5345	8790	11,367·5	14,541
$10^2\Delta_{12}$ ...	6·124	10·94	14·63	17·62	18·91	5·903	7·836	10·33	12·14	14·48
	Solute: chlorobenzene					*Solute: bromobenzene*				
$10^5 f_2$	2582	4507	5881	8502	9969	1333	2736·5	4487	6260·5	8236
$10^2\Delta_{12}$ ...	6·041	7·942	9·441	11·18	12·54	5·246	6·882	8·194	10·42	11·71
	Solute: iodobenzene					*Solute: nitrobenzene*				
$10^5 f_2$	2037	4597	6828	8288	11,733	1905	3249	4929	7105	10,818
$10^2\Delta_{12}$ ...	6·195	9·722	12·33	13·87	17·35	5·694	7·181	9·341	10·91	13·32
	Solute: benzonitrile					*Solute: nitromethane*				
$10^5 f_2$	2465	4937	7542	9559	14,643	5666	10,035	13,181	18,117	22,723
$10^2\Delta_{12}$ ...	7·114	10·56	12·97	14·90	18·49	4·177	4·675	5·019	5·683	6·032

* $\Delta_1 = 0{\cdot}0346$ for $f_2 = 0$.

TABLE 2. *Calculation of molecular anisotropies of solutes at infinite dilution.*

Solute	R.H.S. of equation giving $\Delta\Delta_{12}$	D *	$_\infty\delta_2{}^2 \times 10^3$
$C_6H_5{\cdot}CH_3$	$0{\cdot}7156f_2 - 0{\cdot}155f_2{}^2$	−0·7505	35·27
C_6H_5F	$0{\cdot}8448f_2 - 0{\cdot}631f_2{}^2$	−0·5874	41·52
C_6H_5Cl	$1{\cdot}087_5f_2 - 1{\cdot}85f_2{}^2$	−0·4475	52·94
C_6H_5Br	$1{\cdot}292f_2 - 3{\cdot}46f_2{}^2$	−0·0921	62·49
C_6H_5I	$1{\cdot}449f_2 - 2{\cdot}26f_2{}^2$	+0·2929	69·79
$C_6H_5{\cdot}NO_2$	$1{\cdot}324f_2 - 3{\cdot}80f_2{}^2$	−0·3607	64·09
$C_6H_5{\cdot}CN$	$1{\cdot}561f_2 - 3{\cdot}68f_2{}^2$	−0·6304	75·22
$CH_3{\cdot}NO_2$	$0{\cdot}1298f_2 - 0{\cdot}066f_2{}^2$	−0·2707	8·38

* D is a density coefficient given by $d_{12} = d_1 + Df_2$

Discussion.—(*a*) The values of $_\infty\delta_2{}^2$ given in Table 2 are considerably smaller than δ^2_{gas} but approximately equal to δ^2_{liquid} in the four cases where Δ_{gas}, Δ_{liquid}, and β (the isothermal compressibility) are all known (see Table 3). Since Le Fèvre and Rao [3] have already found the same relation among a number of non-polar solutes, it may therefore be recognised as a general principle.

TABLE 3. *Values of* $\delta^2 \times 10^3$ *for the gaseous, liquid, and dissolved states.*

Substance	$10^3\delta^2_{gas}$	$10^3\delta^2_{liquid}$	$10^3\,{}_\infty\delta_2{}^2$	Substance	$10^3\delta^2_{gas}$	$10^3\delta^2_{liquid}$	$10^3\,{}_\infty\delta_2{}^2$
C_6H_5Cl	86·6	61·2	52·9	$C_6H_5{\cdot}CH_3$ ...	75·4	40·8	35·3
C_6H_5Br	94·2	63·7	62·5	$C_6H_5{\cdot}NO_2$ ...	109·4	71·6	64·1

Data for δ^2_{gas} and δ^2_{liquid} are values selected from the literature by Bhagavantam.[5]

(*b*) We can now recalculate the semi-axes of the polarisability ellipsoids for the monosubstituted benzenes from the molar Kerr constants and electronic polarisations recorded previously.[1,2] The result is in Table 4; it may be claimed for the b's listed on the right-hand side of Table 4(*C*) that they are based entirely on experiment and do not depend upon any assumptions such as Le Fèvre and Le Fèvre made on an earlier occasion.[1] For toluene, b_2 emerges as greater than b_1, and for fluorobenzene b_1 and b_2 are roughly the same, but with the remainder of the substances no serious differences are seen between the

[4] Le Fèvre and Le Fèvre, *Australian J. Chem.*, 1954, **7**, 33.
[5] Bhagavantam, "Scattering of Light and the Raman Effect," Andhra Univ., Waltair, 1940.

TABLE 4. *Calculation of polarisability semi-axes for molecules of type* C_6H_5X.

(*A*) *Basic data*

Group X	T	$(\theta_1 + \theta_2) \times 10^{24}$	$_DP$ (c.c.)	$_EP$ (c.c.)	μ (D)	$_\infty\delta_2^2 \times 10^3$
Me	25°	$3{\cdot}04_4$	32·7	29·9	0·34	$35{\cdot}2_7$
F	20	$13{\cdot}5_1$	31·3	24·9	1·38	$41{\cdot}5_2$
Cl	20	$34{\cdot}4_3$	34·9	29·9	1·59	$52{\cdot}9_4$
Br	25	$40{\cdot}6_4$	35·6	32·6	1·51	$62{\cdot}4_9$
I	20	$42{\cdot}2_2$	41·4	38·3	1·39	$69{\cdot}7_9$
NO_2	20	255·2	36·2	30·9	3·95	$64{\cdot}0_8$
CN	20	272·8	33·1	30·2	4·02	$75{\cdot}2_2$

(*B*) *Calculations of* θ_1 *and* θ_2

Group X	$(b_1 + b_2 + b_3) \times 10^{23}$	$\Sigma(b_1 - b_l)^2 \times 10^{46}$	$_DP/_EP$	$\theta_1 \times 10^{25}$	$\theta_2 \times 10^{25}$
Me	3·555	0·4457	1·094	2·634	0·410
F	2·961	0·3640	1·257	2·514	11·00
Cl	3·555	0·6691	1·167	4·290	30·19
Br	$3{\cdot}876_5$	0·9391	1·092	5·540	35·12
I	4·554	1·4474	1·081	8·596	35·63
NO_2	3·674	0·8651	1·172	5·570	249·6
CN	3·591	0·9700	1·096	5·743	267·0

(*C*) *Semi-axes obtained by using* $_\infty\delta_2^2$ *compared with those (in parentheses) given in J.*, 1954, 1577

Group X	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$
Me	$(1{\cdot}37_7)$	$(1{\cdot}25_3)$	(0·904)	$1{\cdot}27_5$	$1{\cdot}40_1$	$0{\cdot}87_9$
F	$(1{\cdot}12_6)$	$(1{\cdot}10_4)$	(0·711)	$1{\cdot}12_9$	$1{\cdot}13_0$	$0{\cdot}70_3$
Cl	$(1{\cdot}47_2)$	$(1{\cdot}24_4)$	(0·818)	$1{\cdot}47_8$	$1{\cdot}25_5$	$0{\cdot}82_1$
Br	$(1{\cdot}68_4)$	$(1{\cdot}21_2)$	(0·956)	$1{\cdot}68_2$	$1{\cdot}30_1$	$0{\cdot}89_2$
I	$(1{\cdot}98_4)$	$(1{\cdot}40_7)$	(1·136)	$1{\cdot}97_1$	$1{\cdot}58_8$	$0{\cdot}99_6$
NO_2	$(1{\cdot}60_4)$	$(1{\cdot}38_6)$	(0·662)	$1{\cdot}61_7$	$1{\cdot}20_9$	$0{\cdot}86_2$
CN	$(1{\cdot}63_8)$	$(1{\cdot}21_1)$	(0·849)	$1{\cdot}61_6$	$1{\cdot}16_0$	$0{\cdot}81_5$

bracketed and unbracketed figures; b_1 and b_3 for nitrobenzene are now closer to the corresponding values obtained from Stuart and Volkmann's measurements on the vapour than was formerly the case.[6]

Tables 5(*A*) and 5(*B*) are replacements, from the new data of Table 4(*C*), for those published before (pp. 300 and 301 of ref. 2). The semi-axes, not hitherto available, of

TABLE 5. *Recalculation of Tables* 12 *and* 15 *of reference* 2.

(*A*) *Principal axes* * *for* C–X *links in various methyl and phenyl compounds*

C–X in	b_L^{CX}	b_T^{CX}	b_V^{CX}	C–X in	b_L^{CX}	b_T^{CX}	b_V^{CX}
CH_3F	$0{\cdot}12_5$	0·04	0·04	C_6H_5F	0·08	0·08	0·03
CH_3Cl	0·32	0·22	0·22	C_6H_5Cl	0·43	$0{\cdot}20_5$	0·15
CH_3Br	$0{\cdot}46_5$	0·31	0·31	C_6H_5Br	0·63	0·25	0·22
CH_3I	0·68	0·47	0·47	C_6H_5I	0·92	0·54	0·33
$CH_3{\cdot}CN$	0·35	0·18	0·18	$C_6H_5{\cdot}CN$	0·57	0·11	$0{\cdot}14_5$
$CH_3{\cdot}NO_2$	0·34	0·28	0·23	$C_6H_5{\cdot}NO_2$	0·57	0·15	0·19
$CH_3{\cdot}CH_3$	0·30	0·22	0·22	$C_6H_5{\cdot}CH_3$	$0{\cdot}22_5$	0·35	0·21

* In units = 10^{-23} c.c.

(*B*) *Directed exaltations* * *in* C_6H_5X *shown as* $b_i = (b_i^{CX})_{aryl}$ *minus* $(b_i^{CX})_{alphyl}$

Substituent	b_L	b_T	b_V	Substituent	b_L	b_T	b_V
F	$-0{\cdot}04_5$	+0·04	−0·01	CN	+0·22	−0·07	$-0{\cdot}03_5$
Cl	+0·11	$-0{\cdot}01_5$	−0·07	NO_2	+0·23	−0·13	−0·04
Br	$+0{\cdot}16_5$	−0·06	−0·09	CH_3	$-0{\cdot}07_5$	+0·13	−0·01
I	+0·24	+0·07	−0·14				

* In units = 10^{-23} c.c.

the polarisability ellipsoid of nitromethane, are also involved; these follow from $_\infty(_mK_2) = 89{\cdot}0 \times 10^{-12}$, $_DP = 18{\cdot}3$ c.c., $_EP = 12{\cdot}0$ c.c., $\mu = 3{\cdot}14$ D (Le Fèvre and Le Fèvre [1]) and $_\infty\delta_2^2 = 8{\cdot}38 \times 10^{-3}$ (Table 2 of this paper) as:

$$10^{23}b_1 = 0{\cdot}530,\ 10^{23}b_2 = 0{\cdot}474,\ 10^{23}b_3 = 0{\cdot}423$$

The argument used in compiling Tables 5(*A*) and (*B*) has been set out in refs. 1 and 2. For methyl, $b_1 = b_2 = b_3 = 0{\cdot}190_5$; for phenyl, $b_1 = b_2 = 1{\cdot}050_5$, $b_3 = 0{\cdot}669_5$ (all $\times 10^{-23}$ c.c.).

* See ref. 2, p. 289.

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Conclusions reached in refs. 1 and 2 are not qualitatively affected by these recalculations except in the case of toluene, for which the chief (positive) exaltation now appears in the b_2 (transverse) direction. On a simple view this seems a resonable consequence of hyperconjugation between H^+ and $^-CH_2{\cdot}C_6H_5$, since in the redistribution of charge within the benzyl structure there are two *ortho*-positions, but only one *para*-position, at which electron excesses are to be expected. An interesting coincidence is that F and the united atom group CH_3, which both show negative exaltation in the longitudinal direction and very little exaltation in the direction perpendicular to the Ar-ring, are isoelectronic and have the same electronic configuration ($1s^2 2s^2 2p^5$), deformation of the orbitals in CH_3 presumably being the main difference.

The authors acknowledge with gratitude finanical assistance received from the Chemical Society and the award of a Scholarship by the Nuffield Foundation (to B. P. R.).

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[*Received, July 15th,* 1957.]

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295. *Molecular Polarisability. The Specific Kerr Constants and Polarisations of Various Polystyrenes dissolved in Carbon Tetrachloride.*

By (MRS.) C. G. LE FÈVRE, R. J. W. LE FÈVRE, and (MISS) G. M. PARKINS.

Styrene, and four polystyrenes with (viscosity) molecular weights up to 250,000, have been examined. Empirical relations between $\log_{10}$ (M_z/M) and ${}_\infty p_2$, r_2, β, or ${}_\infty({}_6K_2)$ can be established. The polystyrenes are considered to be polar molecules with moments given roughly by $\overline{\mu}^2 = 0{\cdot}56N\mu^2$, where N is the number of phenyl groups per molecule and μ is 0·35 D. The anisotropy of polystyrenes diminishes with increase of molecular weight and is always less than that of the monomer. Calculations from link and other polarisabilities indicate that the smaller polystyrenes are relatively more extended than are the larger. Present observations are qualitatively reconcilable with known data concerning the polystyrenes (streaming double refraction, depolarisation of scattered light, etc.).

HITHERTO the shapes or configurations of macromolecules in solution have largely been deduced from viscosity, diffusion, sedimentation, osmotic pressure, dielectric dispersion, light scattering, or flow birefringence. Conclusions from different methods applied to the same solute have not always been consistent, so additional techniques should be valuable. The Kerr effect [1] appears particularly relevant, and we now report results for polystyrenes in carbon tetrachloride. We do not regard these polystyrenes as isotactic.

EXPERIMENTAL

Apparatus and Methods.—These were as described in the references indicated: dielectric constants,[2] electric double refractions,[1,3] extrapolation procedures and calculations.[1,3,4,5] Refractive indexes were measured on an Abbé refractometer. Experimental techniques are described in refs. 1, 3, and 4, wherein also the symbols are defined. Carbon tetrachloride was dried ($CaCl_2$) and fractionated through a 1 m. column packed with glass helices.

Solutes.—Styrene was distilled, to remove stabiliser, before use (b. p. 34—35°/10 mm. or 145°/760 mm.). The four polystyrenes, designated *A*, *B*, *C*, and *D*, were obtained as follows: *A* by the polymerisation of styrene in carbon tetrachloride containing aluminium chloride; [6] *B* by using stannic chloride and Williams's directions; [7] *C* by the heating together at 100° for

[1] Le Fèvre and Le Fèvre, *Rev. Pure Appl. Chem.*, 1955, **5**, 261.
[2] Buckingham, Chau, Freeman, Le Fèvre, Narayana Rao, and Tardif, *J.*, 1956, 1405.
[3] Le Fèvre and Le Fèvre, *J.*, 1953, 4041.
[4] Le Fèvre, "Dipole Moments," Methuen, London, 3rd edn., 1953.
[5] Harris, Le Fèvre, and Sullivan, *J.*, 1953, 1622.
[6] Jordan and Mathieson, *J.*, 1952, 611.
[7] Williams, *J.*, 1938, 246, 1046.

2 hr. of styrene with 1% w/w of benzoyl peroxide. Polymers *A*, *B*, and *C* were purified by precipitation from their solutions in carbon tetrachloride by methanol, filtration, and drying to constant weight. Sample *D* was " Starex," given to us by C.S.R. Chemicals Pty. Ltd. Infrared spectra (of mulls in " Nujol " or solutions in carbon tetrachloride, on a Perkin-Elmer No. 21 spectrometer) conformed with published [8] data for polystyrene and with one another, save that *C* displayed a very weak absorption in the region appropriate to C=O groups. Presumably catalyst fragments were incorporated in the polymer since Barson and Bevington [9] (cf. Bevington and Brooks [10]) found that [*carboxy*-^{14}C]benzoyl peroxide catalyses the production, in benzene at 60°, of radioactive polystyrenes; they conclude that, of the radicals which initiate polymerisation, 85% are benzoate and 15% are phenyl.

TABLE 1. *Dielectric constants* * *and densities* * *of solutions in carbon tetrachloride at 25°.*

Styrene monomer

10^6w_2 ...	5566	10,432	16,418	17,235
ε	—	2·2309	2·2332	2·2336
d_4^{25}	1·5778	1·5724	1·5655	1·5646

Whence $\sum\Delta\varepsilon/\sum w_2 = 0{\cdot}3788$; $\sum\Delta d/\sum w_2 = -1{\cdot}162$

Polystyrene A

10^6w_2 ...	5040	8120	13,100	14,760	21,000	21,420
ε	2·2305	2·2325	2·2361	—	—	—
d^2	1·5805	1·5780	1·5740	1·5731	1·5683$_5$	1·5677

Whence $\sum\Delta\varepsilon/\sum w_2 = 0{\cdot}6893$; $\Delta d = -0{\cdot}7891w_2 + 0{\cdot}035w_2^2$

Polystyrene B

10^6w_2 ...	3806	4210	5621	5876	7870	10,025	11,195	11,600	15,630	21,490
ε	2·2295	2·2302	2·2304	2·2306	2·2333	2·2336	2·2353	2·2355	2·2365	2·2407
d_4^{25}	1·5821	1·5809	1·5810	1·5807	1·5787	1·5783	1·5770	1·5762	1·5740	1·5699

Whence $\Delta\varepsilon = 0{\cdot}7422w_2 - 5{\cdot}19w^2$; $\Delta d = -0{\cdot}6809w_2 + 0{\cdot}168w_2^2$

Polystyrene C

10^6w_2 ...	4420	5508	5817	7818	9099	9728	10,863	12,472	13,200	15,873
ε	2·2298	2·2306	2·2306	2·2318	2·2325	2·2327	2·2328	2·2335	2·2339	2·2349
d_4^{25}	1·5821	1·5813	1·5808	1·5806	1·5791	1·5782	1·5784	1·5771	1·5775	1·5763

Whence $\Delta\varepsilon = 0{\cdot}7107w_2 - 14{\cdot}0w_2^2$; $\Delta d = -0{\cdot}6471w_2 + 7{\cdot}39w_2^2$

Polystyrene D

10^6w_2 ...	4150	4662	5937	6412	7165	8245	10,376	13,106	13,341	13,572
ε	2·2297	2·2299	—	2·2312	2·2320	—	2·2335	2·2352	2·2357	—
d_4^{25}	1·5815	1·5813	1·5804	1·5807	1·5796	1·5788	1·5779	1·5774	1·5761	1·5749
10^6w_2 ...	15,335	17,084	22,176	25,850	28,002					
ε	—	—	—	2·2433	—					
d_4^{25}	1·5738	1·5725	1·5689	1·5665	1·5633					

Whence $\sum\Delta\varepsilon/\sum w_2 = 0{\cdot}6407$; $\Delta d = -0{\cdot}5724w_2 - 0{\cdot}062w_2^2$

* For $w_2 = 0$, $\varepsilon = 2{\cdot}2270$, $d_4^{25} = 1{\cdot}5845$.

Molecular weights were estimated viscosimetrically at 25°, the equations used being, for benzene solutions [6] of *A*:

$$(\eta_{sp}/c)_{c\to 0} = 0{\cdot}0115 + 1{\cdot}81 \times 10^{-5}M$$

(where c is the concentration in g. per 100 c.c. of solution), for carbon tetrachloride solutions [7] of *B* and *C*:

$$\eta_{sp}/c = 2{\cdot}5 \times 10^{-2}n + 0{\cdot}2$$

(where c is the concentration in base-moles l.$^{-1}$ and n is the average degree of polymerisation), and for carbon tetrachloride solutions [11] of " Starex ":

$$(\eta_{sp}/c)_{c\to 0} = 1{\cdot}7 \times 10^{-4}M^{0{\cdot}69}$$

(where c is in g. per 100 c.c.).

[8] American Petroleum Institute Research Project 44, Nat. Bur. Stand., Washington, 1950, No. 171.
[9] Barson and Bevington, *J. Polymer Sci.*, 1956, **20**, 133.
[10] Bevington and Brooks, *ibid.*, 1956, **22**, 257.
[11] Outer, Carr, and Zimm, *J. Chem. Phys.*, 1950, **18**, 830.

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Experimentally, the left-hand sides of the above equations were respectively 0·0269, 0·798$_5$, 2·12$_5$, and 0·902 (for *A* and *D* extrapolation [12] was performed graphically, and for *B* and *C* the values shown are means of η_{sp}/c), whence weight-average molecular weights are 900 for *A*, 2500 for *B*, 8000 for *C*, and 250,000 for *D*.

TABLE 2. *Electric birefringences and refractive indexes of solutions in carbon tetrachloride* * *at* 25°.

Styrene monomer

10^5w_2 ...	1081	1894	1957	3564	4186	5435
$10^7\Delta B$ ...	0·020	0·035	0·039	0·067	0·084	0·106
$10^4\Delta n_D$ ...	16	29	29	52	62	79

Whence $10^7\Delta B = 1{\cdot}88_5w_2 + 1{\cdot}4_4w_2^2$; $\Sigma\Delta n/\Sigma w_2 = 0{\cdot}147$

Polystyrene A

10^5w_2 ...	701	897	1476	2100	2142	2384	2863
$10^7\Delta B$ ...	0·006	0·008	0·013	0·017$_5$	0·018	—	0·021
$10^4\Delta n_D$ ...	—	—	—	45	46	52	—

Whence $10^7\Delta B = 1{\cdot}010w_2 - 9{\cdot}13w_2^2$; $\Sigma\Delta n/\Sigma w_2 = 0{\cdot}216$

Polystyrene B

10^5w_2 ...	274	322	508	1147	1526	2014	2518
$10^7\Delta B$ ...	—	0·003	0·005	0·011	0·012	0·015	0·018
$10^4\Delta n_D$ ...	6	—	9	22	32	—	—

Whence $10^7\Delta B = 1{\cdot}00_1w_2 - 11{\cdot}9w_2^2$; $\Sigma\Delta n/\Sigma w_2 = 0{\cdot}200$

Polystyrene C

10^5w_2 ...	1007	1528	2173	2477	2532	2970	3588	3872
$10^7\Delta B$ ...	0·005	0·008	0·016	0·018	0·018	0·019	0·021	0·022
$10^4\Delta n_D$ ...	—	—	—	54	54	62	72	

Whence $10^7\Delta B = 0{\cdot}773_6w_2 - 4{\cdot}76w_2^2$; $\Sigma\Delta n/\Sigma w_2 = 0{\cdot}209$

Polystyrene D

10^5w_2 ...	716	717	777	946	1573	1743	2097	2111	2294	3722
$10^7\Delta B$ ...	0·004	0·004	0·006	0·009	0·011	0·012	0·014	0·014	0·019	0·025
$10^4\Delta n_D$ ...	—	—	15	—	37	—	—	51	—	82

Whence $10^7\Delta B = 0{\cdot}752_1w_2 - 1{\cdot}94w_2^2$; $\Sigma\Delta n/\Sigma w_2 = 0{\cdot}226$

* For $w_2 = 0$, $B_1 = 0{\cdot}070 \times 10^{-7}$, $n_D^{25} = 1{\cdot}4575$.

Dielectric constants, densities, electric birefringences, and refractive indexes for the monomer and polystyrenes *A*, *B*, *C*, and *D*, are recorded in Tables 1 and 2. Table 3 presents results.

TABLE 3. *Specific polarisations, refractions, and Kerr constants at infinite dilution in carbon tetrachloride.*

Solute	M_2	$(\alpha\varepsilon_1)_{w=0}$	$(\beta)_{w=0}$	γ	$(\delta)_{w=0}$	$_\infty p_2$ (c.c.)	r_2 (c.c.)	$10^{12}{}_\infty(_sK_2)$
Styrene	104·1	0·379	−0·733	0·101	26·93	0·3577	0·3462	0·212$_5$
Polystyrene *A*	900	0·689	−0·498	0·148	14·43	0·3475	0·3283	0·116
,, *B*	2500	0·742	−0·430	0·137	14·30	0·3405	0·3113	0·114
,, *C*	8000	0·711	−0·408	0·143	11·05	0·3333	0·3106	0·090
,, *D*	250,000	0·641	−0·361	0·155	10·74	0·3172	0·3081	0·087

DISCUSSION

Styrene.—Of the seven references to styrene given by Wesson [13] one deals with the gas and six with the polarisation in solution in benzene. Gorman, Davis, and Gross [14] quote in addition $_TP_{30}$ as 37·9 c.c. in carbon tetrachloride—apparently the only previous result in this solvent. Sakurada and Lee's [15] paper is not cited. Everard, Kumar, and Sutton [16] (since ref. 13 appeared) reported the polarisation in benzene at 25° to be 37·0 c.c.—a value

[12] Martin, *J. Polymer Sci.*, 1953, **10**, 126.
[13] Wessen, "Tables of Electric Dipole Moments," Technology Press, Massachusetts Institute of Technology, 1948.
[14] Gorman, Davis, and Gross, *Physikal. Z.*, 1938, **39**, 181.
[15] Sakurada and Lee, *Z. phys. Chem.*, 1939, *B*, **43**, 245.
[16] Everard, Kumar, and Sutton, *J.*, 1951, 2807.

in harmony with ours (37·2 c.c.) in carbon tetrachloride at the same temperature. Sutton and his co-workers comment on the smallness of moment indicated (R_D is *ca.* 36·5 c.c.) but conclude that it is probably not zero. Von Hippel and Wesson [17] find $\mu = 0{\cdot}12 \pm 0{\cdot}03$ D by the dielectric loss method.

Polystyrenes.—The dielectric polarisation of polystyrenes was examined by Gallay [18] and by Sakurada and Lee.[15] Both investigations were made in benzene as solvent; they disagree in that by the former the specific polarisation of the monomer is less, and by the latter greater, than the observed values for the polymers (see Table 4).

TABLE 4. *Specific polarisations of styrene and polystyrenes in benzene previously reported.*

	Gallay [18]				Sakurada and Lee [15]		
M	104	2820	7750	23,000	104	12,900	42,900
Sp. polarisn. × 10 (c.c.)	3·83	5·74	4·57	3·60	3·678	3·335	3·410

Table 3 shows that, in carbon tetrachloride, ${}_\infty p_2$ diminishes as M increases. A smooth relation between ${}_\infty p_2$ and $\log_{10}(M_x/M)$ (or $\log_{10} M_x$) can be extracted empirically, as also for the specific refraction, density factor β, and specific Kerr constant ${}_\infty({}_sK_2)$ (the last two at infinite dilution). Table 5 summarises these findings, and present equations of possible use in the estimation of molecular weights or degrees of polymerisation, as density or refractive-index measurements are no more difficult to make than those involved in the conventional viscosity method.

TABLE 5. *Relations * between properties and* $\log(M_x/M)$.

Density: $(\beta)_{w_2=0} = -0{\cdot}733 + 0{\cdot}283L - 0{\cdot}052L^2$
Specific refraction: $r_2 = 0{\cdot}346 - 0{\cdot}027L + 0{\cdot}005L^2$
Specific polarisation: ${}_\infty p_2 = 0{\cdot}3577 - 0{\cdot}0104L - 0{\cdot}0006L^2$
Specific Kerr constant: ${}_\infty({}_sK_2) = (0{\cdot}21 - 0{\cdot}11L + 0{\cdot}02L^2) \times 10^{-12}$

Polystyrene	β (calc.)	β (obs.)	r_2 (calc.)*	r_2 (obs.)	${}_\infty p_2$ (calc.)	${}_\infty p_2$ (obs.)	${}_\infty({}_sK_2)$ (calc.)	${}_\infty({}_sK_2)$ (obs.)
A	−0·514	−0·498	0·325	0·328	0·347	$0{\cdot}347_5$	0·13	0·12
B	−0·444	−0·430	0·318	0·311	0·342	$0{\cdot}340_5$	0·10	0·11
C	−0·385	−0·408	0·312	0·311	0·336	0·333	0·08	0·09
D	−0·371	−0·361	0·312	0·308	0·316	0·317	0·08	0·09

* $L = \log_{10}(M_x/M)$.

On the basis of the polarisations listed in Table 3 it is difficult to decide whether polystyrenes should be adjudged polar or non-polar. Were r_2 identical with the specific distortion polarisation, then $\mu = 0{\cdot}22\ [M_2(p_2 - r_2)]^{0{\cdot}5}$ would be, for the monomer and specimens *A*, *B*, *C*, and *D*, in turn, $0{\cdot}2_4$, 0·9, 1·9, 3·0, and *ca.* 10 D. Gallay [18] and Sakurada and Lee [15] proceeded thus and respectively reported moments, rising with molecular weights, from 0·56 to 8·61 (maximum M, 23,000) and 0·1 to 1·83D (maximum M, 42,900). However, in Table 3 one only has to take ${}_DP$ as $1{\cdot}03R$ to make the moment of "Starex" appear zero. In the absence of information concerning the correct ${}_DP/R$ ratios for the polystyrenes it is interesting to apply Debye and Bueche's theory.[19] By this the average moment $\bar{\mu}$ of a polymer molecule is given by:

$$\bar{\mu}^2 = (\mu^2 N)\ [1 + 2p \cos\beta \cos\gamma/(1 - p^2)]$$

where a moment "comes off" every other carbon atom at an angle γ with the preceding C–C bond and an angle β with the following C–C bond, p is the cosine of the valency angle (*i.e.*, 1/3 for a C–C chain), and N is the number of dipoles on the chain; free rotation is assumed (*i.e.*, each chain carbon atom rotates freely on the valency cone, restricted only by the C–C–C bond distances' and angles' being preserved). Insertion of $\beta = ca.\ 70°$ and $\gamma = ca.\ 110°$ requires $\bar{\mu}^2/N\mu^2$ to be 0·92. The obvious value for μ is that for ethylbenzene, whose structure most closely resembles the $-CH_2-CHPh-$ group making up the polystyrenes. Two estimates of $\mu_{\text{ethylbenzene}}$ are available,[13] 0·58 D for the gas and 0·35 D

[17] Von Hippel and Wesson, *Ind. Eng. Chem.*, 1946, **38**, 1121.
[18] Gallay, *Kolloid Z.*, 1931, **57**, 1.
[19] Debye and Bueche, *J. Chem. Phys.*, 1951, **19**, 589.

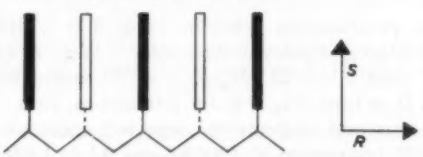
for the liquid. Adopting the lower of these we obtain the figures under $\bar{\mu}_{free}$ in Table 6. Since Debye and Bueche found $\bar{\mu}^2/N\mu^2$ for poly-*p*-chlorostyrene to be 0·56, not 0·92, by experiment, calculations on this basis are also included under $\bar{\mu}_{restr.}$. Rough " order of magnitude " agreement between the three sets of μ's is seen, supporting a conclusion that the polystyrenes are polar molecules.

TABLE 6. *Estimations of mean moments of polystyrenes, complete or limited flexibility being assumed.*

Polystyrene	N	$\bar{\mu}_{free}$	$\bar{\mu}_{restr.}$	$\bar{\mu}_{expt.}$ *
A	9	1·0	0·8	0·9
B	25	1·7	1·3	1·9
C	80	3·0	2·3	2·0
D	2500	17	13	10

* Maximum estimates by uncorrected refractivity method.

Extant evidence on their configurations consistently indicates them to be not completely flexible; detailed information on this point, however, varies. Debye and Bueche [19] infer for poly-*p*-chlorostyrene that the chain repeats itself every four C–C links and that each component moment vibrates about a mean position through a free angle of *ca.* 65°. It is reasonable to suppose that the configuration of a polystyrene will resemble that of its *p*-chloro-derivative. *X*-Ray work [20, 21, 22] has revealed no clear signs of order in *solid* polystyrene, but this is probably irrelevant since it is known that in a solution the solvent can cause uncoiling or extension of the solute.[23] Bueche,[24] from light-scattering studies, decided that polystyrene of *M ca.* 10^6 in benzene or carbon tetrachloride shows a considerable degree of stiffening, corresponding to oscillations around C–C bonds of about 200° instead of the 360° required for complete flexibility. Doty, Affens, and Zimm,[25] by light-scattering and other methods, considered the r.m.s. separations of the ends of polystyrene molecules to be *at least* 3·5 times as large as those expected for " random walk " free-rotation no-hindrance structures. Using scale models of polystyrene, Outer, Carr, and Zimm [11] noted that during intramolecular rotation only about 100° was clear before a phenyl group collided with other portions of the chain.



During the present work measurements of the electric double refraction of polystyrene have been made for the first time (Errera, Overbeck, and Sack [26] having failed to observe an effect with a 10% solution in benzene of a specimen of *M ca.* 30,000). The results in Table 3 provide molar Kerr constants at infinite dilution and molecular refractions; these, combined with the estimates of dipole moments in the fifth column of Table 6, permit calculation of semi-axes of the apparent polarisability ellipsoids for the samples *A* to *D*, provided that two semi-axes are equal to each other. Such an assumption seems intuitively justifiable with molecules as large as those under consideration. It can be formally investigated by imagining a polystyrene chain unfolded to the maximum extent allowed by the normal C–C–C angles (see the Figure, in which phenyl groups and the C–C bonds linking them to the zig-zag backbone are projecting alternately above and below the plane

[20] Katz, *Trans. Faraday Soc.*, 1936, **32**, 86.
[21] Bunn, *J.*, 1947, 297.
[22] Charlesby, *J. Polymer Sci.*, 1953, **10**, 201.
[23] Bawn, " The Chemistry of High Polymers," Butterworths, London, 1948, p. 168.
[24] Bueche, *J. Amer. Chem. Soc.*, 1949, **71**, 1452.
[25] Doty, Affens, and Zimm, *Trans. Faraday Soc.*, 1946, **42***B*, 66.
[26] Errera, Overbeck, and Sack, *J. Chim. phys.*, 1935, **32**, 681.

of the paper at angles of 55°). Polarisabilities along three mutually perpendicular directions R, S, T then follow (by methods often illustrated before [1, 27]) as:

$$b_R = N\,[4b_L^{CC}/3 + 2b_T^{CC}/3 + b_T^{CC} + b_3^{Ph} + 8b^{CH}]$$
$$b_S = N\,[b_L^{CC} + 2b_T^{CC} + b_1^{Ph}/3 + 2b_2^{Ph}/3 + 8b^{CH}]$$
$$b_T = N\,[7b_T^{CC}/3 + 2b_L^{CC}/3 + 2b_1^{Ph}/3 + b_2^{Ph}/3 + 8b^{CH}]$$

where N denotes the number of phenyl groups. Insertion of the values [27, 28] $b_1^{Ph} = b_2^{Ph} = 0{\cdot}733$, $b_3^{Ph} = 0{\cdot}352$, $b_L^{CC} = 0{\cdot}0986$, $b_T^{CC} = 0{\cdot}0274$, $b^{CH} = 0{\cdot}0635$ (all $\times 10^{-23}$ c.c.) then yields $10^{23}b_R = 1{\cdot}037N$, $10^{23}b_S = 1{\cdot}394N$, and $10^{23}b_T = 1{\cdot}371N$. Thus even for the configuration sketched, two semi-axes (S and T) show near-equality and exceed the third (R). Since, in reality, configurations are probably between this extreme on one hand, and a random coil (for which $b_R = b_S = b_T$) on the other, the assumption made above (that two semi-axes are equal) may be safely used to reduce the three " unknowns " (b_1, b_2, b_3) to two ($b_1 = b_2$, b_3). From the geometry of a molecule as in the Figure the resultant dipole moment will act in the direction S; following our usual convention b_1 is therefore along S, b_2 along T, and b_3 along R. The data of Table 3 provide numerical values for $2b_1 + b_3$ and for $\theta_1 + \theta_2$; in its expanded form (see ref. 1) the last quantity can yield the difference $b_1 - b_3$, for which alternative solutions are obtained (as the equation involved is quadratic).

Table 7 shows the individual semi-axes resulting, those produced by taking $b_1 - b_3$ as negative being in parentheses. In the light of the foregoing discussion we believe $b_1 - b_3$ is properly regarded as positive. Table 8 compares the b's so obtained with those required by $b_1 = b_2 = 1{\cdot}38N$, and $b_3 = 1{\cdot}04N$. The predictions are correct in order of magnitude. Table 8 also suggests that the polystyrenes of lower molecular weights are relatively more extended than those of higher molecular weight.

TABLE 7. *Polarisability semi-axes and anisotropies of polystyrenes A, B, C, D.*

Sample	$10^{23} \times (2b_1 + b_3)$	$10^{23}b_1$	$10^{23}b_3$	b_1/b_3 *	$10^3\delta^2$
A	35·1	12·08	10·98	1·10	1·96
		(11·02)	(13·10)		
B	92·5$_5$	31·23	30·09	1·04	0·30
		(29·01)	(34·53)		
C	295·5	98·92	97·63	1·01	0·04
		(94·11)	(106·7)		
D	9159	3054	3051	1·00	*ca.* 0
		(3011)	(3137)		

* b_1/b_3 for the configuration of the Figure is about 1—3.

TABLE 8. *Comparison of semi-axes calculated and found.*

Polystyrene	*A*	*B*	*C*	*D*
N	9	25	80	2500
b_1 (calc.)	12·4	34·5	110	3450
,, (found)	12·1	31·2	98·9	3054
b_3 (calc.)	9·4	26·0	83·2	2600
,, (found)	11·0	30·1	97·6	3051

As the molecular weight rises the anisotropy diminishes. This is displayed by the ratios b_1/b_3 and by the calculated values of $10^3\delta^2$ (Table 7); it is moreover consistent with published observations on the depolarisation of light scattered by polystyrene solutions. Zvetkov,[29] in a study of the polymerisation of styrene, has noted that the optical anisotropy (indicated by depolarisation factors, Δ; see ref. 30 for definitions) of the macromolecules is much less than that of the monomer. Doty and Kaufman,[31] using solutions in toluene and

[27] Le Fèvre and Le Fèvre, *J.*, 1956, 3549.
[28] Le Fèvre and Le Fèvre, *J.*, 1954, 1577.
[29] Zvetkov, *Acta Physicochim. U.R.S.S.*, 1946, **21**, 188.
[30] Le Fèvre and Rao, *J.*, 1957, 3644.
[31] Doty and Kaufman, *J. Phys. Chem.*, 1945, **49**, 583.

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ethyl methyl ketone, report that larger molecules are more isotropic. High scattering power and negligible depolarisation are described by Carr and Zimm [32] for solutions of commercial polystyrenes (Dow Styron) in butanone, dichloroethane, or toluene.

Under the conditions used to detect flow birefringence (cf. review by Cerf and Scheraga [33] for references) polystyrene usually [34] behaves negatively, *i.e.*, the refractive index of the molecule appears less along than across its length. This also is to be expected from calculations above especially if the polymer is additionally stretched from the random-coil type of configuration by the action of the tensions and pressures exerted under the velocity gradients imposed in such experiments (cf. Derf,[35] Zvetkov and Savvon [36]). The flow birefringence of polystyrenes in relation to their molecular weights does not seem to have been fully studied. Zvetkov and Frisman [37] examined monomer–polymer mixtures at different stages of the polymerisation process and found the initially positive birefringences to diminish and change sign as the reaction proceeded. According to Čopič [34] a polystyrene of $M = 3 \times 10^5$ (roughly that of our "Starex") was negative at all velocity gradients in dioxan, although a sample of $M = 8 \times 10^6$ only became negative at higher gradients (when presumably deformation was occurring of what, by inference from Table 7, would seem to be an isotropic, albeit flexible, molecule.

Grateful acknowledgment is made to C.S.R. Chemicals Pty. Ltd. and to Polymer Corporation Pty. Ltd., both of New South Wales, for gifts of chemicals.

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New South Wales, Australia. [*Received, September 23rd*, 1957.]

[32] Carr and Zimm, *J. Chem. Phys.*, 1950, **18**, 1616.
[33] Cerf and Scheraga, *Chem. Rev.*, 1952, **51**, 185.
[34] Čopič, *J. Polymer Sci.*, 1956, **20**, 593.
[35] Cerf, *ibid.*, 1954, **12**, 15, 35.
[36] Zvetkov and Savvon, *Zhur. tekh. Fiz.*, 1956, **26**, 348; *Chem. Abs.*, 1957, **51**, 31e.
[37] Zvetkov and Frisman, quoted in ref. 33.

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296. *Molecular Polarisability. Dependence of Apparent Molar Kerr Constants at Infinite Dilution on the Medium in which they are measured.*

By R. S. Armstrong, M. Aroney, C. G. Le Fèvre, R. J. W. Le Fèvre, and M. R. Smith.

Measurements are reported of the apparent molar Kerr constants of carbon tetrachloride, carbon disulphide, benzene, and naphthalene as solutes in light petroleum, carbon tetrachloride, benzene, and carbon disulphide. Solvent influences are detected and can be correlated with such functions of the refractive index of the solvent as $(n_1^2 - 1)/(n_1^2 + 2)$. It is suggested that the semi-axes of the polarisability ellipsoid of a solute are modified in the presence of a surrounding medium. Four equations, containing empirical terms, are examined whereby "true" semi-axes may be calculated from values secured in carbon tetrachloride, and whereby in turn the apparent semi-axes in other solvents can be computed. Certain consequences such as the predicted increases in molecular anisotropy or electronic polarisation in passing from the liquid or dissolved states to the gas are also considered against the evidence from experiment.

In general, the molar Kerr constant of a compound is a property which may be divided into three [1,2] parts:

$$_mK = 2\pi N(\theta_1 + \theta_2 + \theta_3)/9 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

[1] Le Fèvre and Le Fèvre, *Rev. Pure Appl. Chem.*, 1955, **5**, 261.
[2] Le Fèvre, Le Fèvre, and Narayana Rao, *J.*, 1956, 708.

In eqn. (1), θ_1 is the " anisotropy " term, θ_2 the " dipole " term, and θ_3 is a temperature-independent term. Expansions of θ_1, θ_2, and θ_3 are given in refs. 1—3.* For a non-polar material θ_2 is, of course, zero. Treatments of θ_3, alternative to that of Le Fèvre, Le Fèvre, and Rao,[2] have been devised by Born and Jordan [4] and by Buckingham and Pople.[5] As a consequence of the development of an extrapolation method for the measurement [1,3] of molar Kerr constants of solutes at infinite dilution, the degree to which such ${}_\infty({}_mK_2)$ values are solvent- or state-dependent is obviously important.

Observations by Le Fèvre and Le Fèvre [3,6] have shown that the ratios ${}_\infty({}_mK_2)/({}_mK_{gas})$ and $\mu^2_{solution}/\mu^2_{gas}$ (or ${}_0P_{solution}/{}_0P_{gas}$) are closely similar for substances with moments of 1 D or higher. Since these are cases where θ_2 (in equation 1) greatly exceeds θ_1 and θ_3, Le Fèvre and Le Fèvre [1] have concluded that:

$$(\theta_2)_{solution}/(\theta_2)_{gas} \sim \mu^2_{solution}/\mu^2_{gas}$$

Theoretical considerations (Buckingham [7]) support this. As empirical and other relations now exist [8-10] whereby ratios $\mu_{solution}/\mu_{gas}$ may be predicted *a priori*, the problem is almost solved *where strongly polar solutes in non-polar solvents are concerned.*

Unfortunately very little information exists from which the effects of medium or state on θ_1 or θ_3 can be assessed. Obviously such evidence should be sought among non-polar molecules, otherwise changes in θ_2 could mask those in $\theta_1 + \theta_3$. Three likely sources of data are: (*a*) the comparison of molar Kerr constants calculated from measurements on non-polar gases [11] with those found for the same substances as liquids or solutes; (*b*) the comparison of molecular anisotropies determined for non-polar species in the vapour and liquid states—this follows since the numerator of θ_1 is essentially produced by multiplying the molecular anisotropy by the square of the electronic polarisation, and the latter is known to be a property only very slightly affected by variations of temperature or state (for definitions, formulæ, etc., see Le Fèvre and Purnachandra Rao [12]); and (*c*) the comparisons of ${}_\infty({}_mK_2)$'s found for non-polar solutes in a range of solvents.

Indications from (*a*) and (*b*) suggest that there is considerable change of ${}_mK$ with state: the molar Kerr constants of liquid benzene or carbon disulphide at 25° are $5{\cdot}9 \times 10^{-12}$ or 24×10^{-12} respectively,[1] against these the values for ${}_mK_{gas}$, deduced from the observations by Stuart and Volkmann [11] on the vaporised substances at 113·6° and 56·7°, are *ca.* 17×10^{-12} and 48×10^{-12}; light scattering and depolarisation data published [13] for benzene and carbon disulphide lead to anisotropies as follow:

	$10^{24}\delta^2_{gas}$	$10^{24}\delta^2_{liquid}$
C_6H_6	79·2	37·8
CS_2	221	145

Indications from (*c*) are indefinite. Only Briegleb [14] seems to have dealt with solvent effects where non-polar solutes are involved (see Table 1). Only for CS_2 and C_6H_6 has

* On p. 309 of ref. 1, equation (1) is incorrectly shown without 9 as a denominator and without (26) as its serial number. Other errors which may mislead occur on p. 290, Table 9, where the data for $CHCl_3$ should read 0·673, 9·901, and 0·901; on p. 303, where the angle *A* should be 111° with those at *C* and *D* being 108°; and on p. 305, where the structures shown should be labelled *A*, *B*, and *C* respectively from the top of the page downwards.

[1] Le Fèvre and Le Fèvre, *J.*, 1953, 4041; 1954, 1577.
[4] Born and Jordan, " Elementare Quantenmechanik," Springer Verlag, Berlin, 1930, p. 259.
[5] Buckingham and Pople, *Proc. Phys. Soc.*, 1955, **68**, *A*, 905.
[6] Le Fèvre and Le Fèvre, *J.*, 1955, 2750.
[7] Buckingham, *Trans. Faraday Soc.*, 1956, **52**, 611.
[8] Buckingham and Le Fèvre, *J.*, 1952, 1932.
[9] Le Fèvre, " Dipole Moments," Methuen, London, 1953, 3rd edn., p. 40.
[10] Le Fèvre and Le Fèvre, *Austral. J. Chem.*, 1954, **7**, 33.
[11] Stuart and Volkmann, *Ann. Phys.*, 1933, **18**, 121.
[12] Le Fèvre and Purnachandra Rao, *J.*, 1957, 3644.
[13] Bhagavantam, " Scattering of Light and the Raman Effect," Andhra Univ., Waltair, 1940.
[14] Briegleb, *Z. phys. Chem.*, 1932, **16**, *B*, 249.

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more than one solvent been used; however, Briegleb's remaining $_{\infty}(_{m}K_{2})$'s in heptane may also be compared with determinations made here[3,15] in carbon tetrachloride (1 : 4-$C_6H_4Me_2$ $10{\cdot}6 \times 10^{-12}$, 1 : 4-$C_6H_4Cl_2$ $38{\cdot}6 \times 10^{-12}$, diphenyl 40×10^{-12}, and phenanthrene 83×10^{-12}). In all cases variations are seen, but the changes from solvent to solvent are

TABLE 1. *Molar Kerr constants* ($\times 10^{12}$) *reported* * *by Briegleb.*

	Solutes						
Solvent	CS_2	C_6H_6	$C_{10}H_8$	1 : 4-$C_6H_4Me_2$	1 : 4-$C_6H_4Cl_2$	Ph_2	Phenanthrene
Heptane	30·0	7·8	111·0	15·6	28·2	44·4	114·0
CCl_4	27·0	5·4	—	—	—	—	—
C_6H_6	33·0	—	—	—	—	—	—

* Briegleb's molar Kerr constants are here multiplied by 6 to bring them into relation with those in the present paper.

not consistent throughout, and the extents to which they are due to solvent effects or observational factors are not clear.

Present Work.—At the outset, therefore, it appeared that the most immediately useful contribution would be to establish source (*c*) on a firm experimental basis. To this end, four solutes and four solvents have been systematically examined according to the scheme set out in Table 2, which also includes the $_{\infty}(_{m}K_{2})$'s observed and the considerations which guided the original choice of materials.

TABLE 2. *Solvent effects on* $_{\infty}(_{m}K_{2}) \times 10^{12}$ *for non-polar solutes.*

		Solvents			
		Non-polar and near-isotropic		Non-polar and anisotropic	
Solute	Shape and polarisability of solute	Pet *	CCl_4	C_6H_6	CS_2
CCl_4	Sphere, isotropic	1—2	1—2	1—2	1—2
CS_2	Rod, anisotropic	30·0	27·8	27·1	23·8
C_6H_6	Disc, —„	8·3	7·2	5·9	6·3
$C_{10}H_8$	Flat sheet, anisotropic,	49·4	48·1	45·5	45·0

* Pet = light petroleum, b. p. *ca.* 90°.

Experimental.—Dielectric constants were determined in the circuit used by Buckingham, Chau, Freeman, Le Fèvre, Rao, and Tardif,[16] and electric double refractions by the methods noted in refs. 1 and 3. Symbols and extrapolation procedures have already been fully listed and described respectively by Le Fèvre, Le Fèvre, and Oh,[17] and Le Fèvre and Le Fèvre.[1,3]

Table 3 gives the solvent properties and constants required to proceed from the observ-

TABLE 3. *Solvent properties, constants, etc.*

Solvent	Temp.	10^7B	ε	d	n_D	H	J	$10^{14}{}_{s}K_{1}$
Pet	25°	0·075	1·9449	0·71322	1·3970	1·976	0·5070	2·137
„	30	—	1·9397	0·71042	—	—	—	—
CCl_4	25	0·070	2·2270	1·58454	1·4575	2·060	0·4731	0·749
C_6H_6	25	0·410	2·2725	0·87378	1·4973	2·114	0·4681	7·56
CS_2	25	3·145	2·6246	1·2559	1·6243	2·275	0·4325	31·26

ations, presented in Table 4, to the results shown in Table 5. Materials were as pure as possible, stored over sodium or desiccant as appropriate, and—except naphthalene—redistilled before use. The solvent indicated by " Pet " was a bulk supply of light petroleum (b. p. *ca.* 90°), taken without further treatment other than drying (sodium wire).

[15] Le Fèvre and Le Fèvre, unpublished observations.
[16] Buckingham, Chau, Freeman, Le Fèvre, Rao, and Tardif, *J.*, 1956, 1405.
[17] Le Fèvre, Le Fèvre, and Oh, *Austral. J. Chem.*, 1957, **10**, 218.

TABLE 4. *Kerr constants, refractions, dielectric constants, and densities, of mixtures containing weight fractions w_2 of solute.*

(Temp. = 25°, where not otherwise indicated)

Carbon tetrachloride in light petroleum

10^5w_2	8261	8556	14,437	21,239	25,308	27,144	34,713
Δn	0·0022	0·0023	0·0042	0·0064	0·0078	0·0086	0·0116

whence $\Delta n = 0{\cdot}0251w_2 + 0{\cdot}0240w_2^2$

$10^7\ \Delta B = 0$ at all concentrations examined

10^5w_2	8261	8556	14,437	21,239	25,308	27,144	34,713
ε^{25}	1·9552	1·9558	1·9641	1·9742	1·9792	1·9834	1·9965
d_4^{25}	0·74696	0·74826	0·77448	0·80705	0·82792	0·83789	0·88073

whence $\Delta\varepsilon = 0{\cdot}118w_2 + 0{\cdot}0854w_2^2$
$\Delta d = 0{\cdot}382w_2 + 0{\cdot}288w_2^2$

Carbon tetrachloride in benzene

10^5w_2	6709	13,009	14,749	20,322	25,398	30,466	32,475
$10^7\Delta B$	−0·013	−0·026	−0·027	−0·040	−0·048	−0·062	+0·064
Δn	—	−0·0027	—	—	−0·0056	−0·0063	−0·0076

whence $10^7\Delta B = -0{\cdot}185w_2 - 0{\cdot}043w_2^2$
$\Sigma\Delta n/\Sigma w_2 = -0{\cdot}022$

10^5w_2	6709	13,009	14,749	20,322	25,398	30,466	32,475
ε^{25}	2·2713	—	—	2·2691	2·2687	2·2670	2·2671
d_4^{25}	0·90042	0·92801	0·93496	0·95900	0·98631	1·01125	1·02307

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = -0{\cdot}017$
$\Delta d = 0{\cdot}377w_2 + 0{\cdot}251w_2^2$

Carbon tetrachloride in carbon disulphide

10^5w_2	12,964	13,275	16,945	22,236	25,134	26,693
$10^7\Delta B$	−0·423	−0·429	−0·596	−0·770	−0·850	−0·889
Δn	−0·0191	—	−0·0254	−0·0334	—	—

whence $10^7\Delta B = -3{\cdot}36_2w_2 - 0{\cdot}076w_2^2$
$\Sigma\Delta n/\Sigma w_2 = -0{\cdot}149$

10^5w_2	10,493	12,964	15,605	15,754	16,945	22,236
ε^{25}	2·5828	2·5761	2·5662	2·5643	2·5615	2·5418
d^{25}	1·2818	1·2883	1·2950	1·2955	1·2990	1·3133

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = -0{\cdot}378$
$\Delta d = 0{\cdot}235w_2 + 0{\cdot}104w_2^2$

Carbon disulphide in light petroleum

10^5w_2	1716	3394	6458	7783	9424	13,063	13,812
$10^7\Delta B$	0·026	0·054	0·105	0·127	0·170	0·250	0·271

whence $10^7\Delta B = 1{\cdot}358w_2 + 4{\cdot}33w_2^2$

10^5w_2	3574	6009	8606
Δn	0·0045	0·0076	0·0105

whence $\Sigma\Delta n/\Sigma w_2 = 0{\cdot}1242$

10^5w_2	2582	4770	5696	8103	8811	9071
ε^{30}	1·9484	1·9566	1·9589	1·9677	1·9699	1·9710
d_4^{30}	0·71853	0·72532	0·72786	0·73563	0·73775	0·73877

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 0{\cdot}344$
$\Sigma\Delta d/\Sigma w_2 = 0{\cdot}311$

Carbon disulphide in carbon tetrachloride

10^5w_2	552	1801	2083	3359	3953	4452	4626	5458	8726
$10^7\Delta B$	0·019	0·065	0·073	0·110	0·141	0·145	0·158	0·185	0·303
Δn	0·0005	—	0·0035	0·0058	—	—	0·0084	0·0103	—

whence $10^7\Delta B = 3{\cdot}349w_2 + 1{\cdot}26w_2^2$
$\Sigma\Delta n/\Sigma w_2 = 0{\cdot}1773$

10^5w_2	829	1076	1633	1778	1905
ε^{25}	2·2320	2·2321	2·2345	2·2359	2·2362
d_4^{25}	1·58043	1·57894	1·57676	1·57610	1·57586

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 0{\cdot}494$
$\Sigma\Delta d/\Sigma w_2 = -0{\cdot}4793$

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TABLE 4. (*Continued.*)

Carbon disulphide in benzene

10^5w_2	2009	3308	4982	7370	9976	17,773	
$10^7\Delta B$	0·028	0·058	0·086	0·135	0·196	0·359	
10^5w_2	2837	4982	7370	11,942			
Δn	0·0022	0·0037	0·0057	0·0090			

whence $10^7\Delta B = 1{\cdot}716w_2 + 1{\cdot}761w_2^2$
$\Sigma\Delta n/\Sigma w_2 = 0{\cdot}076$

10^5w_2	2232	2994	3256	3608	4918
ε^{25}	2·2802	2·2808	2·2819	2·2828	2·2866
d_4^{25}	0·87953	0·88133	0·88221	0·88277	0·88623

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 0{\cdot}293$
$\Sigma\Delta d/\Sigma w_2 = 0{\cdot}253_8$

Benzene in light petroleum

10^5w_2	3882	8646	10,952	15,522	15,685	23,473	34,382
$10^7\Delta B$	0·012	0·024	0·037	—	0·056	0·087	0·127
Δn	—	—	0·0081	0·0117	—	0·0181	0·0273

whence $10^7\Delta B = 0{\cdot}324w_2 + 0{\cdot}145w_2^2$
$\Sigma\Delta n/\Sigma w_2 = 0{\cdot}0773$

10^5w_2	10,952	15,522	15,685	20,529	23,473	34,382
ε^{20}	1·9661	1·9769	1·9766	1·9890	1·9977	2·0268
d_4^{20}	0·72372	0·72962	—	0·73549	0·74002	0·75464

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 0{\cdot}2446$
$\Sigma\Delta d/\Sigma w_2 = 0{\cdot}1253$

Benzene in carbon disulphide

10^5w_2	5260	8167	9637	12,959	15,105	17,152	19,826
$10^7\Delta B$	−0·252	−0·401	−0·487	−0·630	−0·735	−0·828	−0·979

whence $10^7\Delta B = -4{\cdot}894w_2 + 0{\cdot}008w_2^2$

10^5w_2	3850	8167	9637	15,105	23,031
Δn	−0·0079	−0·0165	−0·0192	−0·0291	−0·0423

whence $\Sigma\Delta n/\Sigma w_2 = -0{\cdot}1923$

10^5w_2	3850	8167	9637	15,105	23,031	30,478
ε^{25}	2·6078	2·5850	2·5806	2·5558	2·5191	2·4884
d_4^{25}	1·2336	1·2096	1·2016	1·1731	1·1348	1·1008

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = -0{\cdot}455$
$\Delta d = -0{\cdot}587w_2 + 0{\cdot}257w_2^2$

Naphthalene in light petroleum

10^5w_2	3146	5543	7622	9777	10,947	13,088
$10^7\Delta B$	0·039	0·082	0·097	0·141	0·150	0·184
Δn	—	0·0087	—	0·0161	—	0·0217

whence $10^7\Delta B = 1{\cdot}321w_2 + 0{\cdot}646w_2^2$
$\Sigma\Delta n/\Sigma w_2 = 0{\cdot}1637$

10^5w_2	1605	2285	3393	4032
ε^{24}	—	1·9550	1·9607	1·9633
d_4^{24}	0·71762	0·71857	0·72105	0·72231

whence $\Sigma\Delta\varepsilon/\Sigma w_2 = 0{\cdot}455$
$\Sigma\Delta d/\Sigma w_2 = 0{\cdot}2411$

Naphthalene in benzene

10^5w_2	1154	3044	4056	4759	4843	4944	5315
$10^7\Delta B$	0·015	0·049	0·065	0·073	0·073	0·074	0·079

whence $10^7\Delta B = 1{\cdot}67_4w_2 - 3{\cdot}21w_2^2$

10^5w_2	4843	8674	17,010	24,800
Δn	0·0053	0·0093	0·0188	0·0277

whence $\Sigma\Delta n/\Sigma w_2 = 0{\cdot}110$

10^5w_2	3762	4843	6341	8674	17,010	24,800
ε^{25}	2·2855	2·2877	2·2924	2·3009	2·3287	2·3561

whence $\Delta\varepsilon = 0{\cdot}318w_2 + 0{\cdot}077w_2^2$

10^5w_2	1501	3030	4082	4843	8674	17,010	24,800
d_4^{25}	0·87588	0·87801	0·87944	0·88051	0·88577	0·89730	0·90870

whence $\Sigma\Delta d/\Sigma w_2 = 0{\cdot}139$

TABLE 4. (*Continued.*)

Naphthalene in carbon disulphide

$10^5 w_2$	5186	8423	11,028	11,686	14,111	16,856
$10^7 \Delta B$	−0·025	−0·045	−0·077	−0·090	−0·161	−0·217

whence $10^7 \Delta B = -0{\cdot}194 w_2 - 8{\cdot}84 w_2^2$

$10^5 w_2$	4139	9401	10,597	15,982
Δn	−0·0002	−0·0005	−0·0006	−0·0008

whence $\Sigma \Delta n / \Sigma w_2 = -0{\cdot}0052$

$10^5 w_2$	4139	7150	9401	10,597	12,645	15,982
ε^{25}	2·6285	—	2·6328	2·6345	—	2·6392
d_4^{25}	1·2441	1·2358	1·2297	1·2262	1·2211	1·2120

whence $\Sigma \Delta \varepsilon / \Sigma w_2 = 0{\cdot}0912$
$\Sigma \Delta d / \Sigma w_2 = -0{\cdot}278$

TABLE 5. *Calculation of molar Kerr constants at infinite dilution.*

Solute	Solvent	$(a\varepsilon_1)_{w_1=0}$	$(\beta)_{w_1=0}$	γ	$(\delta)_{w_1=0}$	$\infty({}_mK_2) \times 10^{12}$
CCl_4	Pet	0·118	0·535	0·018	0	1·3
CCl_4	C_6H_6	−0·017	0·431	−0·015	−0·452	1·6
CCl_4	CS_2	−0·378	0·187	−0·092	−1·069	1·2
CS_2	Pet	0·344	0·438	0·089	18·11	30·0
CS_2	CCl_4	0·494	$-0{\cdot}302_5$	0·122	47·84	27·8
CS_2	C_6H_6	0·293	$0{\cdot}290_5$	0·051	4·185	27·1
C_6H_6	Pet	0·245	0·176	0·055	$4{\cdot}32_0$	8·3
C_6H_6	CCl_4 *	0·227	−0·755	0·067	10·5	7·2
C_6H_6	CS_2	−0·455	−0·467	−0·118	$-1{\cdot}55_4$	6·3
$C_{10}H_8$	Pet	0·455	0·338	0·117	17·61	49·4
$C_{10}H_8$	CCl_4 †	0·617	−0·515	0·181	49·0	48·1
$C_{10}H_8$	C_6H_6	0·318	0·160	0·073	$4{\cdot}08_3$	45·5
$C_{10}H_8$	CS_2	0·091	−0·221	−0·003	−0·062	45·0

* Data from *J.*, 1954, 1577. † Data from *J.*, 1955, 1641.

Discussion.—Because of the difficulties experienced in measuring near-zero molar Kerr constants, the results with carbon tetrachloride as solute cannot be fixed with certainty between the limits 1—2 × 10^{-12}; with the other solutes, however, definite solvent effects can be discerned. The data of Table 2 give fairly satisfactory plots against the volume polarisations of the solvents or such functions of n_1 as $n_1^2/(n_1^2 + 2)$. The Figure shows $\infty({}_mK_2)$ *versus* $(n_1^2 - 1)/(n_1^2 + 2)$ as an example.

Various considerations, set out in the papers of Raman and Krishnan,[18] and Le Fèvre and Narayana Rao,[19] suggest that the above relations are not accidental, since the apparent semi-axes of polarisability of a molecule may be affected by the properties of the medium in which they are studied and by the shape of the ellipsoidal cavity the structure is assumed to occupy.

Following the work of ref. 19, equation (2) is proposed for non-polar solutes:

$$b_i^s/b_i^v = 3n_1^2/\{(n_1^2 + 2)(1 - f_i b_i^v)[n_1^2 + (1 - n_1^2)k_i]\}. \quad . \quad . \quad . \quad (2)$$

in which the b_i's are the usual three semi-axes of a molecular polarisability ellipsoid, either as they appear in a solution (b_i^s) or as their " true " values in a gas (b_i^v), n_1 is the refractive index of the solvent, the k_i's are shape factors, and the f_i's are quantities given by:

$$f_i = 3k_i(1 - k_i)(n_1^2 - 1)/abc[n_1^2 + (1 - n_1^2)k_i]$$

where *abc* is the product of the radii defining the volume of the cavity. Since Le Fèvre and Narayana Rao [19] obtained reasonable results in a related problem by computing *abc* from the minimum volume of the solute in the liquid state, *i.e.*, $abc = 3M_2/4\pi N d_{mp}$, d_{mp} being the density at the m. p., this method has been adopted here. The k_i's have been read from

[18] Raman and Krishnan, *Proc. Roy. Soc.*, 1928, *A*, **117**, 589.
[19] Le Fèvre and Narayana Rao, *Austral. J. Chem.*, 1955, **8**, 329.

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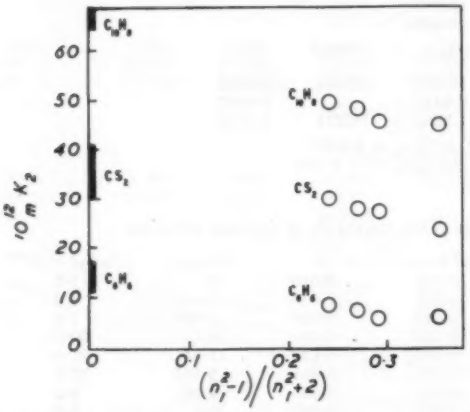
curves due to Osborn,[20] in conjunction with ratios B/A and C/A, in which A, B, and C are linear dimensions derived by calculation, or from scale-drawings, in the way described by Barclay and Le Fèvre,[21] Buckingham and Le Fèvre,[8] and Holland and Le Fèvre [22] (cf. also refs. 1 and 9). For a spherical molecule, of course, $k_1 = k_2 = k_3 = \frac{1}{3}$. Table 6 lists data for the solutes examined. Table 7 gives the polarisability semi-axes deduced from the



Plot of $10^{12}{}_mK_2$ *against* $(n_1^2 - 1)/(n_2^2 + 2)$. *The thick lines on the ordinate show the ranges of* ${}_mK_{gas}$ *calculated by equations* (2), (3*a*), (3*b*), *and* (3*c*). *The values for* $C_{10}H_8$ *should extend up to* 93·4.

${}_\infty({}_mK_2)$'s in carbon tetrachloride contained in Table 5; the cases of benzene and naphthalene are brought forward from previous papers, that of carbon disulphide is new (the ${}_EP$ required for this calculation being 20·39 c.c., taken from Le Fèvre and Narayana Rao's work [23]).

With the help of equation (2), the semi-axes of Table 7 can be transformed into others,

TABLE 6. *Shape factors and dimensions of solutes.*

Solute *	A	B	C	k_1	k_2	k_3
CS_2	6·18	3·08	3·08	$0·17_4$	$0·41_3$	$0·41_3$
C_6H_6	6·70	6·70	2·90	$0·21_5$	$0·21_5$	0·57
$C_{10}H_8$	8·98	7·18	2·90	0·16	0·22	0·62

* Carbon tetrachloride, being spherically symmetrical, has $k_1 = k_2 = k_3 = 1/3$.

TABLE 7. *Semi-axes of the apparent polarisability ellipsoids in carbon tetrachloride as solvent.*

Solute	$10^{23}b_1{}^a$	$10^{23}b_2{}^a$	$10^{23}b_3{}^a$
CS_2	1·308	0·558	0·558
C_6H_6 *	1·114	1·114	0·733
$C_{10}H_8$ †	2·15	1·76	1·03

* From *J.*, 1954, 1577. † From *J.*, 1955, 1641.

TABLE 8. *Semi-axes for molecules in gaseous state, calculated by equation* (2).

	$10^{23}b_1{}^v$	$10^{23}b_2{}^v$	$10^{23}b_3{}^v$
CS_2	1·363	0·525	0·525
C_6H_6	1·214	1·214	0·632
$C_{10}H_8$	$2·41_3$	$1·89_7$	$0·86_3$

$b_i{}^v$ (see Table 8), which should be those found by direct measurement on vapours. Extant information is too sparse for a check of Table 8 from experiment. The Kerr effect of

[20] Osborn, *Phys. Rev.*, 1945, **67**, 351.
[21] Barclay and Le Fèvre, *J.*, 1950, 556.
[22] Holland and Le Fèvre, *J.*, 1950, 2166.
[23] Le Fèvre and Narayana Rao, *Austral. J. Chem.*, 1954, **7**, 135.

naphthalene has not yet been studied as a gas, but Stuart and Volkmann [24] report $10^{23}b_1$'s for carbon disulphide and benzene respectively as 1·512, 0·550, 0·550, and 1·231, 1·231, 0·635. Since Stuart and Volkmann adopted mean polarisabilities which differ from those used here, comparisons are best made by ratios. This is done in Table 9, from which it is obvious that the calculated semi-axes of Table 8 show a near approach to the Stuart and Volkmann's " gas " values.

TABLE 9. *Ratios of semi-axes found and calculated for gases and observed in carbon tetrachloride.*

	Carbon disulphide			Benzene		
	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$	$10^{23}b_1$	$10^{23}b_2$	$10^{23}b_3$
From ref. 24	2·75	1	1	1·94	1·94	1
From Table 7	2·34	1	1	1·52	1·52	1
From Table 8	2·60	1	1	1·92	1·92	1

Next, from the semi-axes of Table 8, and again by using equation (2), the " apparent " semi-axes which the solutes should exhibit in light petroleum, benzene, and carbon disulphide may be computed, and therefrom estimates made of the molar Kerr constants to be expected in these media. Table 10 shows the outcome of such calculations. Agreement between prediction and observation is good for carbon disulphide, somewhat less so for benzene, and worst for naphthalene. This is not surprising, since the assumptions which underlie equation (2)—especially those associated with linear dimensions, shape

TABLE 10. *Calculations of apparent semi-axes and molar Kerr constants in petroleum ether, benzene, and carbon disulphide.*

Solvent	$10^{23}b_1$*	$10^{23}b_2$*	$10^{23}b_3$*	$10^{12}{}_mK$ calc.	$10^{12}{}_mK$ obs.
Solute: CS_2; $abc = 2·08 \times 10^{-23}$ c.c.					
Pet	1·331	0·562	0·652	29·6	30·0
C_6H_6	1·290	0·555	0·555	27·0	27·1
CS_2	1·230	0·539	0·539	23·9	23·8
Solute: C_6H_6; $abc = 3·47 \times 10^{-23}$ c.c.					
Pet	$1·139_5$	$1·139_5$	0·731	8·3	8·3
C_6H_6	1·097	1·097	0·733	6·6	5·9
CS_2	1·038	1·038	0·727	4·8	6·3
Solute: $C_{10}H_8$; $abc = 5·194 \times 10^{-23}$ c.c.*					
Pet	$2·20_5$	$1·79_8$	$1·02_2$	54·1	49·4
C_6H_6	$2·11_2$	$1·73_3$	$1·03_2$	45·1	45·5
CS_2	$1·99_9$	$1·64_3$	$1·03_6$	35·4	45·0

* $d_{mp} = 0·978$ g./c.c. from ref. 25.

factors, and the products *abc*—are probably least valid for naphthalene, the *C* for which (see Table 6) has been taken equal to that of benzene although in reality it is likely to be greater. If the ratio *C*/*A* were larger, then the differences between the ${}_mK$'s forecast for naphthalene in the three solvents in Table 10 would be reduced. Similar remarks would apply also to benzene, two estimates [26] of the " thickness " of which have been 3·2 and 3·7 Å. These both exceed the value of 2·90 Å used here. However, since no reported " thicknesses " of naphthalene can be found in the literature, the matter will not be pursued now, as the present objective is to explore methods of calculation which utilise, for the various solutes, data which are as consistently accessible as possible.

Other equations (3*a*, 3*b*, and 3*c*) have been investigated as alternatives to (2). They

[24] Stuart and Volkmann, *Ann. Phys.*, 1933, **18**, 121.
[25] Egloff, " Physical Constants of Hydrocarbons," Reinhold, New York, 1947, Vol. IV, p. 81.
[26] Listed by Stuart, " Die Struktur des Freien Molekuls," Springer Verlag, Berlin–Göttingen–Heidelberg, 1952, p. 99.

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differ among themselves only in the values adopted for K: in 3*a*, $K = 1$, in 3*b*, $K = n_1^2$, in 3*c*, $K = n_1$:

$$b_i^s/b_i^v = 1 - K(n_1^2 - 1)(0{\cdot}333 - k_i)/(n_1^2 + 2) \quad . \quad . \quad (3a), (3b), \text{ or } (3c)$$

otherwise symbols have the same meanings as in eqn. (2). The quantity $(0{\cdot}333 - k_i)$ is introduced to reflect the departure of the solute molecule from sphericality. Table 12 illustrates the degrees of success in which ${}_mK_2$'s may be predicted by these three relations. Table 11 gives the b_i^v's, deduced from the measurements in carbon tetrachloride (Table 7), which are necessary for the production of Table 12.

By summing the squares of the differences between ${}_mK$ calc. and ${}_mK$ obs. in Tables 10 and 12 it appears that the order of best fit is (3*a*) superior in turn to (3*c*), to (2), and to (3*b*). In large part, however, this situation is determined by the results for naphthalene, comment

TABLE 11. *Semi-axes for molecules in gaseous state, calculated by equations (3a), (3b), and (3c).*

	Equation	$10^{23}b_1^v$	$10^{23}b_2^v$	$10^{23}b_3^v$		Equation	$10^{23}b_1^v$	$10^{23}b_2^v$	$10^{23}b_3^v$
CS_2	3*a*	1·367	0·546	0·546	$C_{10}H_8$ ...	3*a*	$2{\cdot}25_6$	$1{\cdot}81_6$	0·955
	3*b*	1·440	0·533	0·533		3*b*	$2{\cdot}28_3$	$1{\cdot}88_0$	0·882
	3*c*	1·396	0·541	0·541		3*c*	$2{\cdot}30_7$	$1{\cdot}84_1$	0·924
C_6H_6 ...	3*a*	1·151	1·151	0·688					
	3*b*	1·195	1·195	0·645					
	3*c*	1·169	1·169	0·670					

TABLE 12. *Calculations of apparent semi-axes and molar Kerr constants in light petroleum, benzene, and carbon disulphide using equations (3a), (3b), and (3c).*

Solvent	Equation	$10^{23}b_1^s$	$10^{23}b_2^s$	$10^{23}b_3^s$	$10^{12}{}_mK$ calc.	$10^{12}{}_mK$ obs.
			Solute: CS_2			
Pet	3*a*	1·315	0·556	0·556	28·8	30·0
,, ...	3*b*	1·332	0·553	0·553	29·3	,,
,, ...	3*c*	1·322	0·556	0·556	29·3	,,
C_6H_6	3*a*	1·303	0·559	0·559	27·7	27·1
,, ...	3*b*	1·290	0·561	0·561	25·6	,,
,, ...	3*c*	1·298	0·560	0·560	27·2	,,
CS_2	3*a*	1·290	0·561	0·561	26·5	23·8
,, ...	3*b*	1·227	0·573	0·573	20·6	,,
,, ...	3*c*	1·268	0·566	0·566	24·6	,,
			Solute: C_6H_6			
Pet	3*a*	1·119	1·119	0·727	7·7	8·3
,, ...	3*b*	1·129	1·129	0·697	9·1	,,
,, ...	3*c*	1·122	1·122	0·724	7·9	,,
C_6H_6	3*a*	1·111	1·111	0·735	7·1	5·9
,, ...	3*b*	1·103	1·102	0·746	6·2	,,
,, ...	3*c*	1·108	1·108	0·740	6·8	,,
CS_2	3*a*	1·103	1·103	0·746	6·4	6·3
,, ...	3*b*	1·064	1·064	$0{\cdot}787_5$	3·7	,,
,, ...	3*c*	1·090	1·090	0·761	5·4	,,
			Solute: $C_{10}H_8$			
Pet	3*a*	$2{\cdot}16_4$	$1{\cdot}76_9$	$1{\cdot}02_2$	50·4	49·4
,, ...	3*b*	$2{\cdot}19_2$	$1{\cdot}78_2$	$1{\cdot}00_2$	54·9	,,
,, ...	3*c*	$2{\cdot}17_6$	$1{\cdot}77_3$	$1{\cdot}01_5$	52·1	,,
C_6H_6	3*a*	$2{\cdot}14_2$	$1{\cdot}75_5$	$1{\cdot}03_4$	47·3	45·5
,, ...	3*b*	$2{\cdot}11_4$	$1{\cdot}74_5$	$1{\cdot}05_9$	43·4	,,
,, ...	3*c*	$2{\cdot}13_4$	$1{\cdot}75_3$	$1{\cdot}04_1$	46·2	,,
CS_2	3*a*	$2{\cdot}12_1$	$1{\cdot}74_5$	$1{\cdot}05_2$	44·1	45·0
,, ...	3*b*	$2{\cdot}00_4$	$1{\cdot}68_8$	$1{\cdot}12_9$	29·9	,,
,, ...	3*c*	$2{\cdot}08_3$	$1{\cdot}72_5$	$1{\cdot}07_7$	39·0	,,

on which has already been made. If the case of naphthalene is omitted the order appears as (3*c*) better than (3*a*), than (2), than (3*b*), while for carbon disulphide alone it is (2) better than (3*c*), than (3*a*), than (3*b*).

Three other subjects of interest arise from the semi-axes in the above Tables. From the data of Tables 8 and 11, the molar Kerr constants for carbon disulphide and benzene as gaseous dielectrics at 25° may be directly calculated. Values emerge as follows:

From Table 8, involving equation (2), ${}_mK_{gas} \times 10^{12} = 35$ for CS_2 and 17 for C_6H_6;
From Table 11, involving equations (3*a*), (3*b*), and (3*c*), ${}_mK_{gas} \times 10^{12} = 34$—41 for CS_2 and 11—15 for benzene.

The only measurements available are those by Stuart and Volkmann [11] to which reference has already been made. Transformation of their observations into ${}_mK$'s for 25° gives *ca.* 48×10^{-12} and *ca.* 17×10^{-12} for CS_2 and C_6H_6 respectively. Agreement thus seems good for benzene and correct in order for carbon disulphide. However, it should be remarked that the quoted experimental work is solitary and urgently requires re-examination, in view of the practical difficulties always inherent in the determination of small Kerr effects—difficulties which are greatly increased by working at elevated temperatures.

The second subject concerns the molecular anisotropies [12, 13] of gases, reference to which has also been made at the outset. From Tables 8 and 11, values of δ^2_{gas} can be computed:

For CS_2, from Table 8 (eqn. 2), $10^3\delta^2_{gas} = 179$
,, C_6H_6 ,, ,, ,, ,, $= 72$
,, $C_{10}H_8$,, ,, ,, ,, $= 140$
,, CS_2, from Table 11 (eqns. 3*a*, 3*b*, 3*c*) $10^3\delta^2_{gas} = 238$—259
,, C_6H_6 ,, ,, ,, ,, $= 48$—67
,, $C_{10}H_8$,, ,, ,, ,, $= 104$—123

Bhagavantam (ref. 13, pp. 54, 55) lists, as most probable, 221, 79, and 145 for $10^3 \times \delta^2_{gas}$ for CS_2, C_6H_6, and $C_{10}H_8$ respectively. However it is clear, *e.g.*, from data cited by Ramakrishna Rao,[27] that considerable variations exist among the results of different observers; this is particularly the case for CS_2 for which $10^3\delta^2_{gas}$, determined by six workers, lies between the limits 204 (Ramakrishna Rao) and 346 (Ganesan [28]). In such circumstances therefore the applicabilities of equations (2), (3*a*), (3*b*), and (3*c*) cannot be adjudged unsatisfactory.

The third subject relates to the dependence of electronic polarisations on state. From the semi-axes listed in Tables 8 and 11 " vapour values " of electronic polarisations should be calculable by the relation: ${}_EP_{gas} = 4\pi N(b_1^{\nu} + b_2^{\nu} + b_3^{\nu})/3$. Table 13 summarises the position and also makes comparison with the corresponding polarisations drawn from the " solution semi-axes " of Table 7. It is seen that in all cases, except CS_2 by equation (2),

TABLE 13. *Electronic polarisations of* CS_2 *and* C_6H_6 *as vapours and as solutes in carbon tetrachloride.*

	CS_2	C_6H_6	CS_2	CS_2	CS_2	C_6H_6	C_6H_6	C_6H_6
Table and equation involved	8(2)	8(2)	11(3*a*)	11(3*b*)	11(3*c*)	11(3*a*)	11(3*b*)	11(3*c*)
${}_EP_{gas}$ calc.	20·29	25·73	20·68	21·07	20·84	25·15	25·52	25·30
${}_EP_{gas}/{}_EP_{CCl_4}$	0·995	1·033	1·014	1·033	1·022	1·010	1·025	1·016
Table and equation involved	10(2)	10(2)	12(3*a*)	12(3*b*)	12(3*c*)	12(3*a*)	12(3*b*)	12(3*c*)
${}_EP_{liquid}$ calc.	19·41	24·62	20·28	19·96	20·18	24·87	24·81	24·86
${}_EP_{gas}/{}_EP_{liquid}$	1·045	1·045	1·020	1·056	1·033	1·011	1·029	1·018

the electronic polarisation of each species as a gas is forecast to be slightly greater than as a solute. No data exist whereby this can be checked against experiment. However it seems reasonable to assume that ${}_EP_{gas}/{}_EP_{liquid}$ ratios will be close to the corresponding

[27] Ramakrishna Rao, *Ind. J. Phys.*, 1927, **2**, 61.
[28] Ganesan, *Phil. Mag.*, 1925, **49**, 1221.

molecular refraction ratios, which can be found accurately. At N.T.P. and for $\lambda = 5893$ Å, $(n - 1) \times 10^6$ is [29] for CS_2 1478 and for C_6H_6 1823, whence, with $V = 22414{\cdot}6$ c.c., $(R_D)_{gas}$ is 22·08 and 27·23 c.c. respectively; the related $(R_D)_{liquid}$ values [30] are 21·18 and 26·18 c.c., from which $(R_D)_{gas}/(R_D)_{liquid}$ ratios follow as 1·042 and 1·041. The last three lines of Table 13 deal with the ${}_EP_{gas}/{}_EP_{liquid}$ ratios predicted by the four equations under consideration, all of which appear qualitatively correct, while eqn. (2) is nearly quantitatively so.

Finally, the quasi-spherical solute, carbon tetrachloride may be mentioned. For such a structure the k_i's are each 1/3, and it is immediately obvious by equations (3*a*), (3*b*), and (3*c*) that $b_i^s/b_i^v = 1$. By eqn. (2), using $abc = 3{\cdot}64 \times 10^{-23}$ from $d_{mp} = 1{\cdot}67_5$ g./c.c.), $n^2_{CCl_4} = 2{\cdot}1243$, and $b_1^s = b_2^s = b_3^s = 1{\cdot}026 \times 10^{-23}$ (from ${}_EP_{liquid} = 25{\cdot}89$ c.c.), the b_i^v's appear as $1{\cdot}022 \times 10^{-23}$—the ratio b_i^s/b_i^v being thus $1{\cdot}00_4$. Actually, to judge from $(R_D)_{liquid}/(R_D)_{gas}$ values [29, 30] the ratio should be $26{\cdot}51/26{\cdot}58 = 0{\cdot}997_4$. To produce such a result *abc* needs to be $3{\cdot}86_3 \times 10^{-23}$ c.c. which corresponds to $d_{mp} = 1{\cdot}578$; this is far lower than that (1·675 g./c.c.) obtained by extrapolating to −22·9° the densities listed by Timmermans.[31] It is perhaps a coincidence that by using a C–Cl inter-centre distance of 1·76 Å and a " Wirkungs-radius " of 1·6 Å for chlorine,[32] *abc* becomes $3{\cdot}79 \times 10^{-23}$ c.c., a value which makes b_i^s/b_i^v unity. Of course, if ${}_mK_{CCl_4}$ is in fact due to distortion,[3] the assumption that $k_i = 1/3$ is slightly incorrect, and small solvent effects should be expected (see, however, conclusion 7 below).

Conclusions.—(1) The molar Kerr constants of non-polar solutes show a small dependence on the solvent, being larger in media with lower refractive indexes, and *vice versa*.

(2) Such solvent effects can be attributed to apparent variations in the polarisability semi-axes of a molecule caused by its environment.

(3) Equations may be developed whereby the " true " semi-axes can be calculated from corresponding " apparent " values, determined from work on solutions.

(4) In the two cases for which measurements as gases have been made (CS_2 and C_6H_6), the calculated $({}_mK_{gas})$'s are of the order of magnitude found by experiment.

(5) A similar claim may be made regarding the molecular anisotropies as gases of CS_2, C_6H_6, and $C_{10}H_8$.

(6) The equations predict that the electronic polarisations of substances should be slightly greater as vapours than as liquids or solutes; this also is in conformity with known facts regarding molecular refractions.

(7) In the one instance (CCl_4) where the molar Kerr constant is believed to be wholly due to a " θ_3 term," alterations of ${}_mK_2$ by the medium, if they occur at all, are undetectable at the level of experimental accuracy at present available.

The authors acknowledge with gratitude the award of a Research Scholarship to M. R. Smith by the Australian Atomic Energy Commission.

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[29] International Critical Tables, 1930, Vol. VII, 1st edn., p. 10.
[30] Landolt–Börnstein, " Tabellen," 1912 edn.
[31] Timmermans, " Physico-Chemical Constants of Pure Organic Compounds," Elsevier, Amsterdam, 1950.
[32] Stuart, *Z. phys. Chem.*, 1935, *B*, **27**, 350.

297. *The Autoxidation of* trans-11-*Oxoheptadec*-9-*ene*-1-*carboxylic Acid and* trans-11-*Oxoheptadec*-8-*ene*-1-*carboxylic* (12-*Oxoelaidic*) *Acid, with Some Observations on the Autoxidation of Elaidic Acid.*

By George King.

When heated at about 80° in the absence of oxygen, *trans*-11-oxoheptadec-9- and -8-ene-1-carboxylic acid undergo mutual isomerisation, an equilibrium being established in favour of the former, with little or no polymerisation. The rate of autoxidation of these acids with gaseous oxygen at this temperature is of the same order as that of elaidic or oleic acid. No epoxide is formed, nor much active peroxide, but considerable amounts of oxygenated oily products of high molecular weight were obtained on prolonged oxidation. These appear to consist of esters and, possibly, stable peroxides of the perdioxan type.

Preliminary evidence suggests that αβ-unsaturated keto-acids may be formed under certain conditions by decomposition of hydroperoxides in autoxidised elaidic acid.

The formation of conjugated olefin-ketonic acids during the autoxidation of oleic and elaidic acids and their alkyl esters is now well established,[1,2,3] although none appears to have been isolated in a pure state. Considerable interest attaches to the origin and rôle of these αβ-olefin-ketones in the autoxidation process. It has been suggested[4] that they result from hydroperoxides by dehydration, a process which commonly requires a metal catalyst (see, *e.g.*, Farmer and Sundralingam[5]). In the uncatalysed autoxidation of oleic and elaidic acid at moderate temperatures maximum formation of peroxides always precedes that of αβ-unsaturated ketonic acids, but in the presence of cobalt the peroxide concentration remains uniformly low.[2] However, carbonyl formation is independent of a catalyst and its maximum concentration little affected by the presence of cobalt. Ellis[1] considered that 8- and 11-oxo-oleic and -elaidic acid are primary oxidation products, which give rise to dimeric and polymeric oils and resins and readily take up oxygen to form reactive peroxides which play an essential part in the autoxidation process. He found[6] that 12-oxo-oleic acid also is particularly susceptible to atmospheric oxidation, affording high yields of peroxide together with a crystalline product which was later shown to be 11 : 12-dioxo-oleic acid.[7]

Studies in this field are further complicated by the possibilities of double-bond migration,[8,9] *cis-trans*-isomerisation,[9,10] the formation of peroxides other than hydroperoxides,[11,12] and polymerisation. This paper is concerned primarily with the autoxidation of the readily accessible 12-oxoelaidic acid (I) and the isomer *trans*-11-oxoheptadec-

(I) $CH_3\cdot[CH_2]_5\cdot CO\cdot CH_2\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$ $CH_3\cdot[CH_2]_5\cdot CO\cdot CH{:}CH\cdot[CH_2]_8\cdot CO_2H$ (II)

9-ene-1-carboxylic acid[6] (II), which are closely related to the ketonic acids (III) and (IV) occurring in autoxidised elaidic acid. When the acid (I) was heated for several days at

[1] Ellis, *Biochem. J.*, 1950, **46**, 129.
[2] King, *J.*, (*a*) 1954, 2114; (*b*) 1956, 587.
[3] Feuell and Skellon, *J.*, 1954, 3414.
[4] Swern and Coleman, *J. Amer. Oil Chemists' Soc.*, 1955, **32**, 700.
[5] Farmer and Sundralingam, *J.*, 1942, 121.
[6] Ellis, *J.*, 1950, 9.
[7] King, *J.*, 1950, 2897.
[8] Swern, Scanlan, and Ault, *J. Amer. Chem. Soc.*, 1945, **67**, 1132; Ross, Gebhart, and Gerecht, *ibid.*, 1949, **71**, 282; Khan, *Canad. J. Chem.*, 1954, **32**, 1149; *J. Chem. Phys.*, 1954, **22**, 2090; Skellon and Thruston, *J.*, 1953, 138; Blekkingh, Janssen, and Keppler, *Rec. Trav. chim.*, 1957, **76**, 35.
[9] Knight, Eddy, and Swern, *J. Amer. Oil Chemists' Soc.*, 1951, **28**, 188.
[10] Khan, *Biochim. Biophys. Acta*, 1955, **16**, 159.
[11] Treibs, *Ber.*, 1942, **75**, 1373; 1943, **76**, 670; Farmer, *Trans. Faraday Soc.*, 1946, **42**, 228; O'Neill, *Chem. and Ind.*, 1954, 384.
[12] Swern, Coleman, Knight, Ricciuti, Willits, and Eddy, *J. Amer. Chem. Soc.*, 1953, **75**, 3135.

about 80° in the absence of oxygen, the isomer (II) was formed by migration of the double-bond, an equilibrium mixture containing 60—70% of (II) being obtained (Table 1).

TABLE 1. *The effect of heat on the unsaturated oxo-acids.*

	Original acids		After heating under N_2 at 78° for 7 days	
	(I)	(II)	(I)	(II)
M. p.	73°	50·5°	44—49°	44—47·5°
Equiv. wt.	296	296	314	315
M (in dioxan)	296	296	300	314
$E^{1\%}_{1\,cm.}$ at 224 mμ	6	540	339	367
$E^{1\%}_{1\,cm.}$ at 272·5 mμ	2	0·5	2	6
Octanone on saponification (%)	37·5	38	36·8	36·2
Iodine value	120	86	115	98
Carbonyl (%)	9·46	9·46	9·44	9·25

The change was conveniently followed spectroscopically, the strong absorption at 224 mμ being due almost exclusively to the conjugated chromophore CO·CH:CH.[2] Virtually the same mixture resulted on heating the acid (II) and the process was unaffected by the addition of cobalt. Nichols [13] converted acid (I) into (II) by refluxing it for a few minutes with acetic acid containing a trace of sulphuric acid. Therefore, although some migration of the double bond may occur in the acids (III) and (IV) during the autoxidation

(III) $CH_3{\cdot}[CH_2]_6{\cdot}CO{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$ $\quad$ $CH_3{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}CO{\cdot}[CH_2]_6{\cdot}CO_2H$ (IV)

of oleic or elaidic acid, this is not likely to be extensive, as the equilibrium favours the conjugated system; in any case the further oxidation of these acids readily accounts for the formation of small quantities of octanoic and suberic acid, as well as nonanoic and azelaic acid, which constitute important cleavage products of the autoxidation.[14] It is significant that little or no polymerisation occurred under the influence of heat alone.

The autoxidation of 12-oxoelaidic acid (I), m. p. 73°, by gaseous oxygen at 78—80° was accompanied by a rapid increase in the absorption of ultraviolet light at 224 mμ, as a result of its isomerisation to (II), reaching a maximum ($E^{1\%}_{1\,cm.}$ 185) in about 24 hours. The final products (Table 2) were very similar to those obtained by the autoxidation of the

TABLE 2. *The products of the autoxidation of the oxo-acids at* 78—80° (a) *for* 5 *days without a catalyst,* (b) *for* 3 *days with* 0·5% *of cobalt.*

	(I)		(II)	
	a	*b*	*a*	*b*
Physical condition	Viscous yellow oil	Very viscous red oil	Pale yellow semi-solid	Very viscous red-brown oil
Equiv. wt.	251	289	209	237
Iodine value	36	53	21	28
$E^{1\%}_{1\,cm.}$ at 224 mμ	110	109	100	86
$E^{1\%}_{1\,cm.}$ at 272·5 mμ	38	36	13	23
Octanone on saponification with 0·5N-NaOH (%)	4·1	4·0	6·8	4·0
Saponification value	130	141	—	93
Carbonyl (%)	4·0	3·1	6·0	5·0
Oxiran-O (%)	0·0	0·0	0·0	0·0
Active O (%)	0·1	0·06	0·18	0·03
Steam-volatile acids: mequiv. (%)	73	57	109	68
Steam-volatile acids: as heptanoic (%)	9·5	7·4	14·2	8·85
Non-volatile, water-soluble acids, mequiv. (%)	90	57	123	82
as azelaic [from (I)] or sebacic [from (II)] (%)	8·5	5·4	12·4	8·3
CO_2 evolved (%)	3·4	4·3	4·8	4·5
Formic acid evolved as vapour (%)	1·0	0·8	1·7	0·9

isomer (II), although this appeared to be oxidised rather more rapidly and to suffer greater cleavage than (I). The catalytic influence of the cobalt was not marked. At no time

[13] Nichols, *Chem. Abs.*, 1953, **47**, 9999; U.S.P. 2,623,888/1952.
[14] Ellis, *Biochem. J.*, 1936, **30**, 753.

was a high concentration of reactive peroxide (measured by Lea's method) observed, the highest value found for active oxygen being only 0·28%, obtained by oxidising the acid (II) for 2 days at 78°, and much lower values were recorded in the presence of the catalyst (cf. King [2]). The amounts of carbon dioxide and formic acid evolved, as well as the total extent of cleavage, were of much the same order as with oleic and elaidic acids,[2] but in contrast no evidence of epoxide formation was obtained.

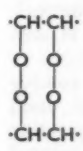
Prolonged oxidation of the oxo-acids yielded considerable amounts of viscous, coloured oils of high molecular weight, but more or less normal equivalent weight, sparingly soluble in light petroleum or carbon tetrachloride (Table 3). These resinous oils were highly oxygenated, corresponding to an absorption of about one molecule of oxygen per molecule of oxo-acid, but had very low epoxide values as measured by the usual methods. Their saponification values (excluding acid values) indicated a consumption of 1—2 equivalents of alkali per mole, and their iodine values the presence of 0·5—2 double bonds. Sebacic acid was formed on saponification of the fraction of high molecular weight isolated

TABLE 3. *Fractions of high molecular weight isolated after autoxidising the oxo-acids at* 80° (a) *for* 3 *days*; (b) *with* 0·5% *of* Co *for* 3 *days*; (c) *for* 5 *days*; (d) *with* 0·5% *of* Co *for* 5 *days*.

Origin	(I) a	(I) b	(II) c	(II) d
Physical nature	Viscous pale yellow oil	Resinous reddish oil	Viscous yellow oil	Resinous red-brown oil
Composition (%) * C	65·3	66·88	64·03	—
Composition (%) * H	8·95	9·05	8·98	—
Equiv. wt.	291	327	259	290
M (in dioxan)	605	940	530	850
$E^{1\%}_{1\,cm.}$ at 224 mμ	84	95	52	69
$E^{1\%}_{1\,cm.}$ at 270 mμ	38	45	23	36
Octanone on saponification (%)	4·0	1·4	2·9	1·2
Iodine value	48	50	20	32
Saponification value	190	170	182	116
Carbonyl (%)	3·7	3·4	4·1	2·5
Active O (%)	0·2	0·1	0·2	0·1
Saponification products: Volatile acids, mequiv. (%)	134	79	98	49
Saponification products: Volatile acids, as heptanoic (%)	17·4	10·3	12·7	6·4
Saponification products: Non-volatile, water-soluble acids, mequiv. (%)	—	192	280	99
Saponification products: Non-volatile, water-soluble acids, as sebacic (%)	—	19·4	28·3	10·0

* Calc. for $C_{18}H_{30}O_5$: C, 66·2; H, 9·3%. Calc. for $C_{18}H_{32}O_5$: C, 66·7; H, 8·7%.

from autoxidised (II), and it seems probable that such fractions are composed partly of esters of dibasic acids, analogous to, but not identical with, the esters occurring in autoxidised oleic or elaidic acid.[1,2] The composition and high molecular weight of the resinous fractions suggest the presence also of polymeric peroxides of the perdioxan type, (*A*), which are relatively stable structures.[11] All these fractions reduced Fehling's solution, but had a much reduced carbonyl content and yielded little octanone on hydrolysis. A low content of the conjugated enone group, CO·CH:CH, was also indicated by the relatively small absorption of ultraviolet light at 224 mμ. On the other hand, the absorption curves all showed an inflexion or feeble maximum at *ca.* 270 mμ, which has previously been encountered in autoxidised unsaturated fatty acids and their derivatives and is usually attributed to small amounts of triply conjugated systems, such as ·CO·CH:CH·CO·[15] (or its enolic form) or ·CH:CH·CH:CH·CO·.[16] The author has observed a similar shoulder ($E^{1\%}_{1\,cm.}$ 7 at 270 mμ) in oleic acid containing 0·4% of cobalt through which oxygen had been bubbled for 28 days at room temperature.



(*A*)

[15] Holman, Lundberg, Lauer, and Burr, *J. Amer. Chem. Soc.*, 1954, **67**, 1285.

[16] Evans and Gillam, *J.*, 1945, 432; Bolland and Koch, *J.*, 1945, 445; Parkinson and Skellon, *J.* 1957, 851; cf. Jones and Lahey, *Univ. Queensland Papers, Dept. Chem.*, 1942, **1**, 22; *Chem. Abs.*, 1943, **37**, 3342.

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The mechanism of the formation of the conjugated unsaturated ketonic acids in autoxidised elaidic acid is still not clear. Preliminary experiments on the oxidised acid have shown that thermal decomposition of the peroxides is strongly catalysed by cobalt, but that this is accompanied by a definite increase in the content of carbonyl conjugated with the double bond only when the acid has been oxidised at low temperature (Table 4). Further work on this problem is being done.

TABLE 4. *The effect of heat on the products obtained by autoxidising elaidic acid* (a) *at* 50° *for* 15 *days*; (b) *at* 80° *for* 24 *hr.*

	Before heating		After heating under N_2 at 80° for 90 min.			
			Alone		With 0·5% of Co	
	(a)	(b)	(a)	(b)	(a)	(b)
Active O (%)	0·52	0·44	0·41	0·33	0·008	0·016
$E^{1\%}_{1\,cm.}$ at 224 mμ	21·8	56·2	24·8	54·0	37·7	56·4
8- and 11-Oxoelaidic acids (%)	3·90	10·2	4·44	9·8	6·85	10·3
Total carbonyl (%)	0·78	1·70	0·73	1·51	1·07	1·93
Iodine value	71	38	70	39	69	40
Oxiran-O (%)	0·47	1·06	0·51	1·20	0·25	0·92

EXPERIMENTAL

trans-11-Oxoheptadec-8-ene-1-carboxylic acid (12-oxoelaidic acid) (I), m. p. 73°, was prepared from ricinelaidic acid [6] and was converted into *trans*-11-oxoheptadec-9-ene-1-carboxylic acid (II), m. p. 50·5°, by way of the hydrogen bromide adduct.[17].

Methods.—The methods of autoxidation and analyses of the products were similar to those described in connexion with the autoxidation of oleic and elaidic acid.[3] In the determination of carbonyl, however, it was found necessary to use a pH-meter instead of an indicator in titrations to pH 3·7, owing to the colour of the products. For the same reason a pH-meter was used in the determination of saponification values.

Steam-volatile Acids.—The autoxidation product from acid (I) or (II) was distilled with water as previously described [3a] and the neutralised distillate was evaporated to small bulk. Addition of zinc sulphate solution precipitated zinc heptanoate, which crystallised from pure ethanol in plates, m. p. and mixed m. p. 137·5°.

Non-volatile, Water-soluble Acids.—After removal of the volatile acids, the residual solution was filtered hot and the insoluble oil washed with hot water. The filtrate and washings were evaporated to small bulk and cooled. From acid (I) a small amount of slightly impure azelaic acid was obtained. This crystallised from water in plates, m. p. 102—103°, not depressed by pure azelaic acid. From acid (II) the less soluble sebacic acid was obtained in better yield; it crystallised from hot water in plates, m. p. and mixed m. p. 130—131° (Found: equiv., 103. Calc. for $C_{10}H_{18}O_4$: equiv., 101).

Octan-2-one.—Distillation of acid (I) or (II) with 0·5N-sodium hydroxide afforded octan-2-one as a volatile oil in good yield.[6, 17] The volatile oil similarly obtained from the autoxidised acids gave a 2 : 4-dinitrophenylhydrazone, m. p. 68°, not depressed by octan-2-one 2 : 4-dinitrophenylhydrazone (Found: C, 54·2; H, 6·5; N, 17·6. Calc. for $C_{14}H_{20}O_4N_4$: C, 54·5; H, 6·5; N, 18·2%).

Fractions of High Molecular Weight.—The autoxidised acids were freed from steam-volatile and water-soluble acids, and the residual oils dissolved in ether. The ethereal solution, dried and filtered, was treated with 3 volumes of light petroleum (b. p. 40—60°) and left in a separating funnel for 24 hr. The supernatant solvent was removed by decantation and the precipitated oil was again dissolved in ether and precipitated with light petroleum. The oil was washed with light petroleum, and the residual solvent removed *in vacuo* at 40°. The viscous products were almost insoluble in light petroleum and, unlike the original oxo-acids, very sparingly soluble in carbon tetrachloride. The analytical results are summarised in Table 3.

The author thanks Professor R. T. Williams for his interest in this work.

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PADDINGTON, LONDON, W.2. [*Received, October* 23*rd*, 1957.]

[17] King, *J.*, 1951, 1980.

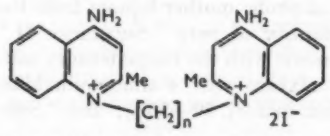
298. *Potential Trypanocides. The Action of Polymethylene Dihalides on 4-Aminoquinaldine.*

By W. C. Austin, M. D. Potter, and E. P. Taylor.

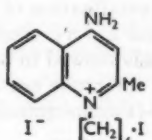
In an attempt to obtain a synthetic trypanocide, a series of polymethylene-bis-(4-aminoquinaldinium salts) was prepared. The decamethylene member was found to be a potent antibacterial agent, and is now commercially available. During the preparation of the hexamethylene homologue, the presence of a highly trypanocidal impurity was demonstrated. This was identified as 4-amino-1-(6-4′-quinaldinylaminohexyl)quinaldinium iodide hydriodide, and a practicable synthesis of it has been developed.

Our recent investigations have shown that heterocyclic polymethylenebis(quaternary ammonium salts) exhibit a wide range of biological activity.[1,2] These compounds have symmetrical molecules with relatively large end-groups, a feature which is also present in many compounds active against trypanosomiasis (the so-called " butterfly "[3] or " dumb-bell-shaped "[4] structure). Consequently, the possible therapeutic action of a simple series, the polymethylenebis(*iso*quinolinium salts), was examined in mice infected with *Trypanosoma congolense*. Slight activity was demonstrated, highest in the hexamethylene compound.

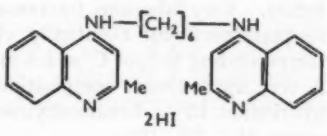
Since the decamethylene chain was the most readily available, we next prepared a series of basically substituted heterocyclic decamethylenebis(quaternary ammonium salts), with the intention of later shortening the chain length of the most promising compounds. One of the first compounds made was decamethylenebis-(4-aminoquinaldinium iodide) (I), since several synthetic trypanocides are derivatives of 4-aminoquinaldine.[5] This was



(I; n = 10) (II; n = 8) (III; n = 6)



(IV)



(V)

appreciably active against *T. congolense*; it also possessed high antibacterial and antifungal activity,[6] and the chloride, given the approved name of " dequalinium chloride " by the General Medical Council, is commercially available under the name " Dequadin ". Reduction of the chain length increased the trypanocidal activity in infected mice. The octamethylene homologue (II), at a dose of 10 mg./kg., was approximately as active against *T. rhodesiense* in mice as was suramin and stilbamidine, although it was less effective at a dose of 1 mg./kg. The product from the reaction of 4-aminoquinaldine with hexamethylene di-iodide, on recrystallisation from ethanol–ether, gave satisfactory analyses for the expected hexamethylene bis-(4-aminoquinaldinium iodide) (III) and appeared particularly active against *T. congolense* in mice. It was therefore prepared on a larger scale, but the product, after recrystallisation from ethanol or ethanol–methanol, while still giving satisfactory analyses, had a slightly higher melting point but an unexpectedly low trypanocidal activity (less than the crude material before recrystallisation). The original high activity might thus have been due to impurities.

Fractional crystallisation of the crude reaction mixture was difficult but, although

[1] Taylor, *J.*, (*a*) 1951, 1150; (*b*) 1952, 142; (*c*) 1952, 1309.
[2] Collier, Potter, and Taylor, *Brit. J. Pharmacol.*, (*a*) 1953, **8**, 34; (*b*) 1955, **10**, 343.
[3] Goble, *J. Pharmacol.*, 1950, **98**, 49.
[4] Walls, *Chem. and Ind.*, 1951, 606.
[5] Jensch, *Angew. Chem.*, 1937, **50**, 891.
[6] Babbs, Collier, Austin, Potter, and Taylor, *J. Pharm. Pharmacol.*, 1956, **8**, 110.

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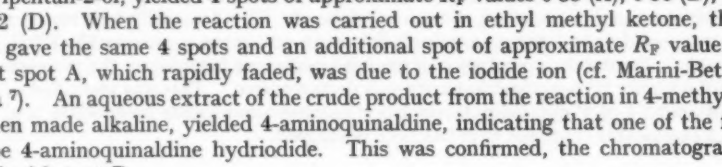
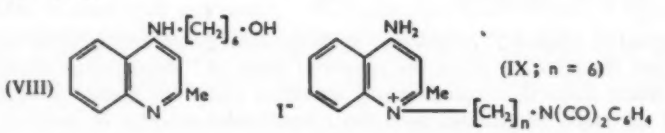
complete separation was not originally achieved, pharmacological testing of different fractions indicated that at least three substances were present. Since the second fraction was most active against *T. congolense* (and had low toxicity), it was considered to contain the active impurity, which we provisionally called " Substance II."

Paper-chromatographic separation of the crude mixture obtained by reaction in 4-methylpentan-2-ol, yielded 4 spots of approximate R_F values 0·35 (A), 0·56 (B), 0·63 (C), and 0·72 (D). When the reaction was carried out in ethyl methyl ketone, the crude product gave the same 4 spots and an additional spot of approximate R_F value 0·8 (E). The first spot A, which rapidly faded, was due to the iodide ion (cf. Marini-Bettolo and Miranda [7]). An aqueous extract of the crude product from the reaction in 4-methylpentan-2-ol, when made alkaline, yielded 4-aminoquinaldine, indicating that one of the fractions might be 4-aminoquinaldine hydriodide. This was confirmed, the chromatogram being identical with spot D.



Repeated recrystallisation (from methanol–ethanol) of the water-insoluble residue yielded the pure product corresponding to spot B, whose analysis and reactions (*e.g.*, reprecipitation by the addition of sodium iodide to an alkaline solution) showed it to be the originally required hexamethylenebis-(4-aminoquinaldinium iodide) (III). This compound was also prepared, although in exceedingly small yield, by the action of hexamethylene di-iodide on 4-acetamidoquinaldine, followed by acid hydrolysis and addition of potassium iodide. Very laborious fractional crystallisation of the alcoholic mother-liquors from the bisquaternary salt eventually yielded a very small quantity of pure " Substance II " corresponding to spot C, which analysis showed to be isomeric with the bisquaternary salt. A very approximate composition of the crude reaction mixture was: 4-aminoquinaldine hydriodide, 15%; hexamethylenebis-(4-aminoquinaldinium iodide), 70—75%; and " Substance II ", 15—10%.



Fractional crystallisation of the crude product from the reaction in ethyl methyl ketone yielded the fourth product, corresponding to spot E, which was identified by synthesis, mixed melting point, and chromatography as the monoquaternary salt, 4-amino-1-6′-iodohexylquinaldinium iodide (IV).

From the analysis of " Substance II ", several structures were possible, *e.g.* (V), (VI), and (VII).

The hydrochloride corresponding to the salt (V) was readily synthesised by interaction of hexamethylenediamine and 4-chloroquinaldine, but the corresponding dihydriodide differed from " Substance II." Since chromatography indicated the total absence of product (V) from the crude reaction mixture, it was originally considered unlikely that " Substance II " would possess the related structure (VI), and considerable work on the synthesis of the isomer (VII) was therefore carried out. This proved extremely difficult and has not yet been accomplished, although work continues.

Consequently the synthesis of the asymmetrical compound (VI) was investigated.

[7] Marini-Bettolo and Miranda, *Rend. Ist. sup. San.*, 1954, **17**, 463.

6-Aminohexanol reacted with 4-chloroquinaldine to give 4-6′-hydroxyhexylaminoquinaldine (VIII), which with hydriodic acid gave the hydriodide of the corresponding 6-iodo-compound. Refluxing this with 4-aminoquinaldine in 4-methylpentan-2-ol and fractionating the product gave " Substance II " (m. p., mixed m. p., chromatography, and biological activity), although in poor yield. This proved the presence of a 4-[substituted hexylamino]quinaldine structure, but was obviously not a practicable synthesis of the trypanocide.

Such a synthesis was finally effected as follows: *N*-6-iodohexylphthalimide and 4-aminoquinaldine in boiling ethyl methyl ketone gave the phthalimido-quaternary salt (IX). With hydrazine and hydrochloric acid this yielded the amino-compound, which with 4-chloroquinaldine (alone or in phenol) gave " Substance II " (VI) in excellent yield. The last reaction was also carried out satisfactorily by using 4-phenoxy- or 4-methoxy- in place of 4-chloro-quinaldine, as is to be expected since 4-phenoxyquinolines are intermediates in reactions of 4-chloroquinolines with aliphatic amines in the presence of phenol.[8]

The two synthetic products and " Substance II " were identical in m. p., mixed m. p., chromatography, infrared absorption spectrum, and biological activity. The structure of " Substance II " was confirmed when addition of sodium iodide to its alkaline solution gave the quaternary monoiodide corresponding to (VI). This with alkyl halides yielded the corresponding quaternary salts.

Of several salts of " Substance II " prepared, preliminary field trials in Africa indicate that the chloride (registered name Tozocide) possesses high therapeutic activity against trypanosomiasis in cattle. Other salts are being investigated for prophylactic activity.

NN′-Di-4-quinaldinylhexamethylenediamine dihydriodide (V) had little activity against *T. congolense* or *T. rhodesiense*, although Schock and his collaborators [9] have recently reported that this and some closely related compounds possess curative activity against *T. gambiense* in mice.

In view of the recently reported [10] neuromuscular blocking activity of some quaternary *N*-ω-piperidinoalkylphthalimides, the corresponding activity of some of the 4-amino-1-ω-phthalimidoalkylquinaldinium iodides was investigated. 4-Amino-1-(6-phthalimidohexyl)quinaldinium iodide was approximately half as potent as (+)-tubocurarine chloride in the frog's rectus preparation.

A preliminary report of our work has been published,[11] and full pharmacological details will be described elsewhere by Collier and Smith.

Experimental

Unless otherwise stated, analyses of quaternary ammonium salts were of materials dried at 100° *in vacuo*.

Most of the polymethylenebis(*iso*quinolinium iodides) have been previously described, but the following appear to be new: *Trimethylene*, yellow plates (from methanol–ethanol), m. p. 251—253° (decomp.) (Found: C, 45·6; H, 3·7; N, 5·25; I, 45·5. $C_{21}H_{20}N_2I_2$ requires C, 45·5; H, 3·6; N, 5·05; I, 45·85%). *Tetramethylene*, yellow needles (from methanol), m. p. 247—249° (decomp.) (Found: C, 46·65; H, 3·9; N, 4·8; I, 44·35. $C_{22}H_{22}N_2I_2$ requires C, 46·5; H, 3·9; N, 4·9; I, 44·7%). *Pentamethylene*, yellow plates (from ethanol), m. p. 190—191° (Found: C, 47·4; H, 4·4; N, 4·9; I, 43·6. $C_{23}H_{24}N_2I_2$ requires C, 47·4; H, 4·2; N, 4·8; I, 43·6%). *Hexamethylene*, yellow needles or plates (from methanol–ethanol), m. p. 233—234° (Found: C, 48·5; H, 4·4; N, 4·5; I, 42·3. $C_{24}H_{26}N_2I_2$ requires C, 48·3; H, 4·4; N, 4·7; I, 42·6%). *Heptamethylene*, yellow plates (from 95% ethanol), m. p. 216—217° (Found: C, 49·1, H, 4·65; N, 4·55; I, 41·3. $C_{25}H_{28}N_2I_2$ requires C, 49·2; H, 4·6; N, 4·6; I, 41·6%). These compounds were prepared by refluxing the appropriate polymethylene dihalide with *iso*quinoline (50% excess) in benzene.

[8] Surrey and Cutler, *J. Amer. Chem. Soc.*, 1951, **73**, 2623.
[9] Schock, *J. Amer. Chem. Soc.*, 1957, **79**, 1672; Otto, Moetsch, and Schock, *Amer. J. Trop. Med. Hyg.*, 1957, **6**, 393.
[10] Donahoe, Seiwald, Neumann, and Kimura, *J. Org. Chem.*, 1957, **22**, 68.
[11] Austin, Collier, Potter, Smith, and Taylor, *Nature*, 1957, **179**, 143.

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The following 4-aminoquinaldine salts appear to be new: *Hydrochloride*, needles (from ethanol), m. p. 346—347° (decomp.) (Found: C, 61·1; H, 6·2; N, 14·05; Cl, 18·1. $C_{10}H_{11}N_2Cl$ requires C, 61·7; H, 5·7; N, 14·4; Cl, 18·25%). *Hydrobromide*, needles (from methanol–ethanol), m. p. 335—336° (decomp.) (Found: C, 50·2; H, 5·0; N, 11·7, Br, 33·25. $C_{10}H_{11}N_2Br$ requires C, 50·2; H, 4·6; N, 11·7; Br, 33·5%). *Hydriodide*, needles (from ethanol), m. p. 282—283° (decomp.) (Found: C, 41·7; H, 4·05; N, 9·9; I, 44·25. $C_{10}H_{11}N_2I$ requires C, 42·0; H, 3·9; N, 9·8; I, 44·4%).

Acetylation of 4-Aminoquinaldine.—This was difficult but was carried out by refluxing 4-aminoquinaldine (2 g.), acetic anhydride (4 ml.), and pyridine (8 ml.) for 4 hr., distilling off the bulk of the solvent *in vacuo*, treating the residue with ice-water (20 ml.), and making the whole alkaline with ammonia. After further cooling, the precipitate was filtered off, washed with cold water, and recrystallised from benzene, *4-acetamidoquinaldine* being obtained as needles (2·25 g.), m. p. 162—164° (Found: loss at 100°, 15·4. $C_{12}H_{12}ON_2,2H_2O$ requires 15·25%. Found, in anhydrous material: C, 71·8; H, 6·0; N, 14·4. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·05; N, 14·0%).

Preparation of Polymethylenebis-(4-aminoquinaldinium Salts).—Decamethylenebis-(4-aminoquinaldinium iodide) (I). Decamethylene di-iodide (17·4 g., 1 mol.), 4-aminoquinaldine (16 g., 2·3 mol.), and 4-methylpentan-2-ol (150 ml.) were refluxed for 72 hr., then cooled and filtered, and the solid was washed successively with 4-methylpentan-2-ol, acetone, water, and acetone and dried. The residue was treated in methanol with charcoal, and the solution filtered, concentrated to small bulk, and allowed to crystallise; *decamethylenebis-(4-aminoquinaldinium iodide)* (14·3 g.) was obtained as a cream-coloured microcrystalline powder, m. p. 308—309° (decomp.) (Found: C, 50·6; H, 5·5; N, 7·9; I, 35·6. $C_{30}H_{40}N_4I_2$ requires C, 50·7; H, 5·7; N, 7·9; I, 35·8%). Use of decamethylene dibromide and the same solvent gave the corresponding but colourless *bromide* (from methanol–ethanol), m. p. 326—327° (decomp.) (Found: C, 58·3; H, 6·65; N, 8·95; Br, 26·4. $C_{30}H_{40}N_4Br_2$ requires C, 58·4; H, 6·55; N, 9·1; Br, 26·0%). Reaction in ethanol gave as the only product 4-aminoquinaldine hydrobromide. The following decamethylenebis-(4-aminoquinaldinium salts) were prepared by double decomposition: *Nitrate*, needles (from ethanol–ether), m. p. 299—301° (decomp.) (Found: C, 62·5; H, 7·3; N, 13·9. $C_{30}H_{40}O_6N_6$ requires C, 62·1; H, 6·95; N, 14·5). *Chloride* (from ethanol), m. p. 326° (decomp.) (Found, on material dried at 180° *in vacuo*: C, 68·3; H, 7·8; N, 10·4; Cl, 13·25. $C_{30}H_{40}N_4Cl_2$ requires C, 68·3; H, 7·65; N, 10·6; Cl, 13·5). *Perchlorate* (from methanol–ethanol), m. p. 282—284° (decomp.) (Found: C, 55·0; H, 6·3; N, 8·7; Cl, 10·9. $C_{30}H_{40}O_8N_4Cl_2$ requires C, 55·0; H, 6·2; N, 8·55; Cl, 10·8%).

The salts in Table 1 were prepared in boiling ethyl methyl ketone, the reaction time varying from 100 to 450 hr.

TABLE 1. *Polymethylenebis-(4-aminoquinaldinium iodides)* (cf. I—III).

			Found (%)					Required (%)			
n	Solvent	M. p.*	C	H	N	I	Formula	C	H	N	I
4	M–E †	340—341°	45·7	5·0	8·9	40·0	$C_{24}H_{30}N_4I_2$	46·0	4·5	8·95	40·6
5	M–E	293—294	46·9	4·9	8·6	39·4	$C_{25}H_{30}N_4I_2$	46·9	4·7	8·75	39·7
7	EtOH	297	48·25	5·2	8·5	37·9	$C_{27}H_{34}N_4I_2$	48·5	5·1	8·4	38·0
‡	EtOH	317—318	46·8	4·85	8·0	37·3	$C_{26}H_{32}ON_4I_2$	46·6	4·8	8·4	37·9
8	EtOH	294—295	48·9	5·5	8·1	37·8	$C_{28}H_{36}N_4I_2$	49·3	5·3	8·2	37·2
9	EtOH	288—289	49·8	5·7	8·1	36·6	$C_{29}H_{38}N_4I_2$	50·0	5·5	8·05	36·5
12	M–E	291—292	52·3	5·9	7·5	34·4	$C_{32}H_{44}N_4I_2$	52·0	6·0	7·6	34·4
14	E–Et ¶	266—267	53·5	6·5	7·4	32·7	$C_{34}H_{48}N_4I_2$	53·3	6·3	7·3	33·2
16	EtOH	253—255	54·45	6·3	6·8	31·65	$C_{36}H_{52}N_4I_2$	54·4	6·6	7·05	32·0
18	E–Et	253—254	55·75	6·9	6·8	30·7	$C_{38}H_{56}N_4I_2$	55·5	6·9	6·8	30·9
20	EtOH	241—242	56·0	7·3	6·8	29·5	$C_{40}H_{60}N_4I_2$	56·5	7·1	6·6	29·9

* With decomp. † M–E = MeOH–EtOH. ‡ 4-Oxaheptamethylene, $-[CH_2]_3\cdot O\cdot[CH_2]_3-$. ¶ E–Et = EtOH–$Et_2O$. The *dinitrate* corresponding to the tetradecamethylene compound had m. p. 239—241° (decomp.) (from EtOH–Et_2O) (Found: C, 63·5; H, 7·7; N, 13·2. $C_{34}H_{48}O_6N_8$ requires C, 64·15; H, 7·6; N, 13·2%).

4-Amino-1-6′-iodohexyl- (IV), yellow rosettes (from ethanol–methanol), m. p. 202° (Found: C, 39·1; H, 4·5; N, 5·8; I, 51·0. $C_{16}H_{22}N_2I_2$ requires C, 38·7; H, 4·5; N, 5·65; I, 51·2%) and *4-amino-1-3′-iodopropyl-quinaldinium iodide*, yellow prisms (from ethanol), m. p. 230—231° (Found: C, 34·7; H, 3·6; N, 6·2; I, 55·9. $C_{13}H_{16}N_2I_2$ requires C, 34·4; H, 3·55; N, 6·2; I, 55·95%), were prepared by refluxing 4-aminoquinaldine with 3 mols. of the appropriate

polymethylene di-iodide in ethyl methyl ketone. Treating the latter product with methylamine (0·5 mol.) in methanol for 6 weeks at room temperature yielded a small quantity of *4-methyl-azaheptamethylenebis-(4-aminoquinaldinium iodide)*, m. p. 282° (decomp.) (from methanol) (Found: C, 47·2; H, 5·35; N, 10·4; I, 36·8. $C_{27}H_{35}N_5I_2$ requires C, 47·4; H, 5·2; N, 10·25; I, 37·2%).

Reaction of 4-Aminoquinaldine with Hexamethylene Di-iodide.—Hexamethylene di-iodide (3·5 g., 1 mol.), 4-aminoquinaldine (4·2 g., 2·6 mol.), and 4-methylpentan-2-ol (35 ml.) were refluxed for 156 hr., cooled, and filtered, and the residue was washed three times with 4-methylpentan-2-ol, then repeatedly with acetone, and dried, giving a purplish solid (6·4 g.). This was boiled with water (100 ml.), then cooled. The solid material was collected, and extracted with water (2 × 100 ml.), the mixture being cooled before filtration. The combined aqueous extracts were concentrated to 150 ml., made alkaline with sodium hydroxide solution, kept overnight, and filtered, and the precipitate was washed with cold water and dried, giving crude 4-aminoquinaldine (0·67 g.), m. p. 152—154°. This was dissolved as far as possible in hot benzene (0·07 g. of insoluble material), and the filtrate was concentrated to small bulk and allowed to crystallise; fairly pure 4-aminoquinaldine (0·5 g.), m. p. and mixed m. p. 163°, was obtained.

The dark, water-insoluble residue obtained above was dried (4·15 g.), dissolved in methanol (450 ml.), treated with charcoal, and the whole filtered hot. To the filtrate ethanol (600 ml.) was added, the solution concentrated to 250 ml., a further 350 ml. of ethanol were added, and the solution was concentrated to 40 ml. This was allowed to cool and filtered (and the filtrate *A* retained), and the residue washed with a little ethanol and dried (2·9 g.). This material (m. p. 287—291°) gave little more than single chromatogram spot, corresponding to spot B. Repeated recrystallisation from methanol–ethanol gave cream-coloured *hexamethylenebis-(4-aminoquinaldinium iodide)* (III), m. p. 296—297° (decomp.) (Found: C, 47·5; H, 5·3; N, 8·55; I, 38·4. $C_{26}H_{32}N_4I_2$ requires C, 47·7; H, 4·9; N, 8·6; I, 38·8%). The corresponding *perchlorate* (from methanol–ethanol) had m. p. 263—265° (decomp.) (Found: C, 51·7; H, 5·5; N, 9·1; Cl, 12·1. $C_{26}H_{32}O_8N_4Cl_2$ requires C, 52·1; H, 5·4; N, 9·35; Cl, 11·85%), and the *picrate* (from aqueous acetone) had m. p. 266—268° (Found: C, 53·65; H, 4·5; N, 16·2. $C_{38}H_{36}O_{14}N_{10}$ requires C, 53·3; H, 4·2; N, 16·4%).

The alcoholic filtrate *A* was warmed and treated with warm ether (80 ml.); an oil separated. Next morning the solvent was decanted and rejected. The residual gum was dissolved as far as possible in hot ethanol (30 ml.) and kept overnight. The insoluble residue (0·11 g.; m. p. 265—270°), mainly crude hexamethylenebis-(4-aminoquinaldinium iodide), was rejected. The filtrate was concentrated to 15 ml., and warm ether (30 ml.) added, an oil separating which partly crystallised. The solvent was decanted, and a solution of the residue in the minimum quantity of boiling ethanol treated with warm acetone to turbidity, allowed to crystallise, and filtered. The residue was washed with acetone–ethanol, then with acetone, and dried, giving 0·2 g. of product, m. p. 276—278° (decomp.). Repeated recrystallisation of this from ethanol–acetone gave *Substance II*, m. p. 287—289° (decomp.) (Found: C, 47·7; H, 5·1; N, 8·4; I, 38·2%), giving a chromatogram corresponding to spot C.

Paper Chromatography.—This was carried out with Whatman No. 1 paper, by the descending technique. The most satisfactory mobile phase found was the upper layer of butanol–ethanol–water (30 : 9 : 25); development was best by iodine in chloroform; after drying, the background colour faded, leaving the fractions marked by brown spots.

NN′-Di-4′-quinaldinylhexamethylenediamine Dihydriodide (V).—4-Chloroquinaldine (2·2 g.) and hexamethylenediamine (0·66 g.) were heated on a steam-bath for 3 hr., then at 165° for 8 hr. After cooling, the solid was washed with dry ether, then dissolved in water containing a little hydrogen chloride. The solution was saturated with salt, and the tan-coloured precipitate of the dihydrochloride filtered off. This was re-dissolved in hot water, reprecipitated by 5N-ammonia, collected, and recrystallised from aqueous ethanol. *NN′-Di-4′-quinaldinylhexamethylenediamine* was obtained as needles, m. p. 210—211° (Found: C, 78·0; H, 7·7; N, 14·0. $C_{26}H_{30}N_4$ requires C, 78·4; H, 7·6; N, 14·1%). Addition of sodium iodide to a solution of this base in dilute hydrochloric acid yielded the corresponding tan-coloured *dihydriodide*, m. p. 338—340° (from methanol–ethanol) (Found: C, 47·6; H, 5·05; N, 8·75; I, 38·3. $C_{26}H_{32}N_4I_2$ requires C, 47·7; H, 4·9; N, 8·6; I, 38·8%).

The pale yellow *tetramethylene homologue*, crystallised from methanol–ethanol, had m. p. 305—306° (Found: C, 45·8; H, 4·8; N, 9·1; I, 40·2. $C_{24}H_{28}N_4I_2$ requires C, 46·0; H, 4·5;

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N, 8·95; I, 40·6%), and the buff *decamethylene homologue* (from methanol–ether) m. p. 258—260° (Found: C, 50·5; H, 5·3; N, 8·0; I, 36·0. $C_{30}H_{40}N_4I_2$ requires C, 50·7; H, 5·7; N, 7·9; I, 35·8%); the *base* from the latter formed prisms (from aqueous ethanol), m. p. 178—179° (Found: C, 79·2; H, 8·6; N, 12·2. $C_{30}H_{38}N_4$ requires C, 79·3; H, 8·4; N, 12·3%).

Proof of the Presence of a 4-(*Substituted Hexylamino*)*quinaldine Structure in "Substance II".*—*5-Cyanopentyl acetate.* 5-Chloropentyl acetate [12] (159 g.), sodium iodide (151 g.), and acetone (1100 ml.) were refluxed for 34 hr., the mixture was then filtered, the acetone distilled off, the residue dissolved as far as possible in ether, and after filtration the ether was removed. The resulting crude 5-iodopentyl acetate was dissolved in ethanol (300 ml.), potassium cyanide (70 g.) in water (90 ml.) added, and the stirred mixture heated under reflux for 5 hr. The ethanol was then distilled off and the black liquid residue extracted four times with benzene, each benzene extract being washed successively with the same N-sodium hydroxide solution (50 ml.), and then with water. The combined benzene extracts were shaken with sodium sulphate, filtered, and evaporated, and the residue was distilled *in vacuo*. The fraction boiling at 134—142°/12 mm. (100 g.) was redistilled, giving *5-cyanopentyl acetate* (88 g.), b. p. 135—137°/12 mm. (Found: C, 61·9; H, 8·8; N, 8·65. $C_9H_{13}O_2N$ requires C, 61·9; H, 8·45; N, 9·0%).

6-Aminohexanol. 5-Cyanopentyl acetate (25·6 g.) and liquid ammonia (25 ml.) were heated in a rotating bomb with hydrogen (initial pressure 75 atm.) and Raney nickel. The temperature was raised as rapidly as possible to 140° (pressure rose to 130 atm.), and the bomb then allowed to cool, rotation being continued (pressure dropped to 65 atm.). After filtration and washing of the residue with ether, ethanolic hydrogen chloride was added to the combined filtrate and washings until no more heavy oil separated. Water was then added, the aqueous layer separated, 20% sodium hydroxide solution (200 ml.) added, and the mixture refluxed for 1 hr. After cooling, the clear solution was saturated with potassium carbonate, the oil extracted with chloroform, the extract shaken with anhydrous potassium carbonate, the solvent recovered, and the residue distilled *in vacuo*, giving 6-aminohexanol (15·8 g.), b. p. 126—127°/14 mm. (lit.,[13] 126°/15·3 mm.), needles, m. p. 52—54° (Found: N, 12·0. Calc. for $C_6H_{15}ON$: N, 12·0%). Distillation of the crude hydrogenation product of 5-cyanopentyl acetate without hydrolysis yielded a mixture of 6-aminohexanol and *6-aminohexyl acetate*, b. p. 111—113°/11 mm. (Found: C, 60·7; H, 11·1; N, 9·05. $C_8H_{17}O_2N$ requires C, 60·4; H, 10·8; N, 8·8%). Hydrolysis of this with hydriodic acid (*d* 1·94), followed by neutralisation and acidification with ethanolic hydrogen chloride, gave the hydrochloride of *6-aminohexyl iodide*, plates (from acetone–ether), m. p. 118—119° (Found: C, 27·45; H, 5·7; N, 5·4; Hal, 61·6. $C_6H_{15}NClI$ requires C, 27·3; H, 5·7; N, 5·3; Hal, 61·7%).

4-6′-Hydroxyhexylaminoquinaldine (VIII). 6-Aminohexanol (2 g.) and 4-chloroquinaldine (3 g.) were mixed and heated at 165—170°. When the internal temperature reached 167°, the bath was removed, but the internal temperature rose to 260°, and then fell. The mixture was then heated for a further 30 min. at 165—170°. After cooling, the reddish-orange residue was dissolved in hot ethanol and poured into excess of 2N-sodium hydroxide. The precipitated oil crystallised and was filtered off, washed with water, and dried. On recrystallisation from benzene, *4-6′-hydroxyhexylaminoquinaldine* (3·3 g.) separated as needles, m. p. 134—136° (Found: C, 74·2; H, 8·4; N, 10·9. $C_{16}H_{22}ON_2$ requires C, 74·4; H, 8·6; N, 10·85%). This reaction was more easily controlled in boiling *p*-cymene (10 ml.) but the yield was lower (2·5 g.). 4-Chloroquinaldine, heated with excess of *n*-hexylamine in a sealed tube at 160° for 3 hr. (cf. general method of Fulton and his collaborators [14]), gave *4-hexylaminoquinaldine*, needles [from light petroleum, (b. p. 100—120°)], m. p. 119—121° (Found: C, 79·0; H, 9·0; N, 11·8. $C_{16}H_{22}N_2$ requires C, 79·3; H, 9·2; N, 11·6%).

4-6′-Iodohexylaminoquinaldine hydriodide. 4-6′-Hydroxyhexylaminoquinaldine (4 g.) and hydriodic acid (8 ml.; *d* 1·94) were refluxed with stirring for 2 hr., cooled, and diluted with water, the aqueous layer was decanted and rejected, and the gummy residue washed by decantation with water. It was then dissolved in warm acetone (30 ml.), and ether added to turbidity. After crystallisation, filtration and washing with acetone–ether gave a yellowish residue which, recrystallised from ethanol, gave the required *hydriodide* (5 g.), m. p. 132—134° (Found: C, 38·75; H, 4·6; N, 5·85; I, 50·7. $C_{16}H_{22}N_2I_2$ requires C, 38·7; H, 4·5; N, 5·65; I, 51·2%).

[12] Cason, Wallcave, and Whiteside, *J. Org. Chem.*, 1949, **14**, 37.
[13] Takamoto, *J. Pharm. Soc. Japan*, 1928, **48**, 366.
[14] Fulton, Joyner, King, Osbond, and Wright, *Proc. Roy. Soc.*, 1950, *B*, **137**, 339.

Preparation of "Substance II." 4-6′-Iodohexylaminoquinaldine hydriodide (3 g.) was added to a solution of 4-aminoquinaldine (3 g.) in hot 4-methylpentan-2-ol (60 ml.), and the mixture heated at 110—120° for 48 hr. After cooling, the purplish-brown precipitate was filtered, washed with ethyl methyl ketone, and dried, then washed three times with hot water (the aqueous washings being rejected) in order to remove 4-aminoquinaldine hydriodide. The insoluble residue, which had become gummy, was dissolved in methanol (150 ml.) (charcoal), ethanol (100 ml.) was added to the filtrate, and the whole concentrated to approximately half-bulk. After cooling, a resinous non-crystallisable gum separated, which was rejected. The solution was then concentrated to small bulk, acetone added until cloudy, and left to crystallise. The small quantity (*ca.* 0·2 g.) of material which separated was filtered off and rejected. The filtrate was again concentrated to half-bulk, excess of ether added, and the mixture set aside overnight. The resinous solid (1·7 g.; sinters at 110°) which separated was filtered off and dried. Paper chromatography showed this to be rich in "Substance II". It was dissolved as far as possible in hot ethanol (45 ml.), and the mixture filtered and kept overnight. The small amount of gum which separated was removed, and excess of ether added to the solution. A gum separated which solidified in a few days. This was washed with ether, dried, and dissolved in methanol (30 ml.), ethanol (60 ml.) was added, and the solution concentrated to half-bulk, treated with a further 30 ml. of ethanol and allowed to cool. A small quantity of gum separated, and was removed; acetone was then added until crystals slowly separated. These were filtered off, washed with acetone–alcohol, and dried. The product [0·6 g.; m. p. 276—278° (decomp.)], recrystallised from methanol–ethanol–acetone, gave almost pure "Substance II" (0·2 g.), m. p. 284—286° (decomp.), mixed m. p. 286—288° (decomp.) (Found: C, 48·0; H, 5·1; N, 8·45; I, 38·5%). Further recrystallisation raised the m. p. to 287—289° (decomp.).

Synthesis of "Substance II."—N-6-*Iodohexylphthalimide.* Potassium phthalimide (11·1 g., 1 mol.) and hexamethylene di-iodide (81 g., 4 mol.) were heated at 140—150° for 24 hr., ether (600 ml.) was added, inorganic material filtered off, and the bulk of the solvent recovered. The residue, on cooling, deposited a small quantity (0·3 g.) of phthalimide, which was removed. The excess of hexamethylene di-iodide was then distilled off *in vacuo*, and the residue triturated with light petroleum (b. p. 40—60°) (75 ml.), a solid slowly crystallising. This was filtered, off washed with light petroleum (b. p. 40—60°), dried, and recrystallised from ethanol, giving N-6-*iodohexylphthalimide* as needles, m. p. 76° (14·5 g.) (Found: C, 47·6; H, 4·5; N, 3·8; I, 36·2. $C_{14}H_{16}O_2NI$ requires C, 47·1; H, 4·5; N, 3·9; I, 35·6%).

The following N-ω-*iodoalkylphthalimides* were prepared similarly: butyl, m. p. 87—89° (lit.,[18], 88—89°), *pentyl*, m. p. 73—75° (Found: N, 4·0; I, 36·2. $C_{13}H_{14}O_2NI$ requires N, 4·1; I, 37·0%), *heptyl*, m. p. 42—43° (Found: N, 3·8; I, 34·5. $C_{15}H_{18}O_2NI$ requires N, 3·8; I, 34·2%), *octyl*, m. p. 63—64° (Found: N, 3·7; I, 32·8. $C_{16}H_{20}O_2NI$ requires N, 3·6; I, 33·0%), *nonyl*, m. p. 48—50° (Found: N, 3·6; I, 32·5. $C_{17}H_{22}O_2NI$ requires N, 3·5; I, 31·8%), *decyl*, m. p. 64—65° (Found: N, 3·1; I, 30·0. $C_{18}H_{24}O_2NI$ requires N, 3·4; I, 30·75%), *tridecyl*, m. p. 60—62° (Found: N, 3·1; I, 27·7. $C_{21}H_{30}O_2NI$ requires N, 3·1; I, 27·9%). All formed needles from ethanol.

Owing to the difficulty of removing excess of the higher-boiling polymethylene di-iodides, certain *N*-ω-iodoalkylphthalimides were prepared by heating potassium phthalimide with an equimolecular quantity of di-iodide. Considerable quantities of the αω-diphthalimidoalkanes resulted, the bulk of which separated on cooling of the filtered ethereal solution of the reaction mixture. However it proved extremely difficult to remove the last traces of these compounds from the required products, which were therefore used in the rather crude state in the next reaction, since the diphthalimidoalkanes did not interfere and could be easily removed at this stage. *N*-14-Iodotetradecylphthalimide, m. p. *ca.* 71—73°, and the hexadecyl, m. p. *ca.* 68—70°, octadecyl, m. p. *ca.* 74—76°, and eicosyl, m. p. *ca.* 74—76°, homologues were then prepared.

The following are new: 1 : 16-*diphthalimidohexadecane*, plates (from ethanol), m. p. 116—117° (Found: C, 74·7; H, 8·0; N, 5·35. $C_{32}H_{40}O_4N_2$ requires C, 74·4; H, 7·8; N, 5·4%), and *octadecane*, needles (from ethanol), m. p. 117—118° (Found: C, 74·6; H, 7·8; N, 5·0. $C_{34}H_{44}O_4N_2$ requires C, 75·0; H, 8·15; N, 5·15%), and *eicosane homologues*, needles (from ethanol), m. p. 114—116° (Found: C, 75·4; H, 8·1; N, 4·7. $C_{36}H_{48}O_4N_2$ requires C, 75·5; H, 8·5; N, 4·9%).

[18] Arnstein, Hunter, Muir, and Neuberger, *J.*, 1952, 1329.

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4-Amino-1-6′-phthalimidohexylquinaldinium Iodide (IX).—4-Aminoquinaldine (5·18 g.), *N*-(6-iodohexyl)phthalimide (11·7 g.) and ethyl methyl ketone (50 ml.) were refluxed for 300 hr. After cooling, the precipitate was filtered off, washed with ethyl methyl ketone, and recrystallised from ethanol–methanol, *4-amino-1-6′-phthalimidohexylquinaldinium iodide* (9·8 g.) being obtained as thick needles, m. p. 229—230° (Found: C, 55·9; H, 4·9; N, 8·15; I, 24·55. $C_{24}H_{26}O_2N_3I$ requires C, 55·9; H, 5·1; N, 8·2; I, 24·7%). This compound was also prepared by heating a solution of 4-amino-1-6′-iodohexylquinaldinium iodide (IV) and potassium phthalimide in dimethylformamide for 1 hr. on a steam-bath. The corresponding *perchlorate* crystallised from methanol as needles, m. p. 223—225° (Found: C, 59·0; H, 5·7; N, 8·45; Cl, 7·5. $C_{24}H_{26}O_6N_3Cl$ requires C, 59·1; H, 5·4; N, 8·6; Cl, 7·3%).

4-Amino-1-ω-phthalimidoalkylquinaldinium iodides, prepared by refluxing ethyl methyl ketone solutions of the appropriate *N*-ω-iodoalkylphthalimides and 4-aminoquinaldine for varying times (100—450 hr.), are recorded in Table 2. All formed needles from ethanol (unless otherwise stated).

TABLE 2. *4-Amino-1-ω-phthalimidoalkylquinaldinium iodides* (IX).

		Found (%)					Required (%)			
n	M. p.	C	H	N	I	Formula	C	H	N	I
3	260—262° *	53·05	4·35	8·85	26·7	$C_{21}H_{20}O_2N_3I$	53·3	4·3	8·9	26·85
4	263—264	54·4	4·9	8·8	25·6	$C_{22}H_{22}O_2N_3I$	54·2	4·55	8·6	26·1
5	236—238	55·4	4·8	8·45	25·4	$C_{23}H_{24}O_2N_3I$	55·1	4·8	8·4	25·35
7	170—172	56·0	5·6	7·9	24·25	$C_{25}H_{28}O_2N_3I$	56·7	5·3	7·9	24·0
8	238—240	57·9	6·0	7·9	24·0	$C_{26}H_{30}O_2N_3I$	57·5	5·6	7·7	23·4
9	174—176	57·7	5·45	7·5	23·2	$C_{27}H_{32}O_2N_3I$	58·2	5·8	7·5	22·8
10	189—191 †	58·4	6·1	7·3	22·6	$C_{28}H_{34}O_2N_3I$	58·8	6·0	7·35	22·2
13	142—144	60·5	6·7	7·1	20·6	$C_{31}H_{40}O_2N_3I$	60·7	6·6	6·85	20·7
14	155—156	60·9	6·6	7·2	20·8	$C_{32}H_{42}O_2N_3I$	61·2	6·75	6·7	20·3
16	155—157 ‡	62·5	7·05	6·15	18·9	$C_{34}H_{46}O_2N_3I$	62·3	7·1	6·4	19·4
18	151—152 §	63·25	7·5	6·15	18·6	$C_{36}H_{50}O_2N_3I$	63·25	7·4	6·15	18·6
20	144—146 §	64·0	7·5	5·7	17·7	$C_{38}H_{54}O_2N_3I$	64·1	7·7	5·9	17·9

* Microcryst., from MeOH–EtOH. † The corresponding *bromide* formed needles (from EtOH), m. p. 205—207° (Found: C, 63·6; H, 6·75; N, 7·8; Br, 15·1. $C_{24}H_{26}O_2N_3Br$ requires C, 64·1; H, 6·5; N, 8·0; Br, 15·3%), and the *nitrate* needles (from EtOH), m. p. 170—172° (Found: C, 65·8; H, 6·7; N, 11·3. $C_{28}H_{34}O_5N_4$ requires C, 66·4; H, 6·8; N, 11·1%). ‡ Nodules. § Prisms.

4-Amino-1-(6-4′-quinaldinylaminohexyl)quinaldinium iodide hydriodide (VI) (*"Substance II"*). 4-Amino-6-phthalimidohexylquinaldinium iodide (6·18 g.), methanol (60 ml.), and 90% aqueous hydrazine hydrate (0·66 g.) were heated on a steam-bath under reflux for 1 hr., water (15 ml.) added, and the bulk of the methanol distilled off under reduced pressure. Concentrated hydrochloric acid (15 ml.) was then added, and the mixture heated on a steam-bath for a further 1 hr. After cooling in ice water, the precipitated phthalhydrazide was filtered off, washed with a little ice-water, and rejected. The combined filtrate and washing were evaporated to dryness *in vacuo*, the residue dissolved in the minimum quantity of water, and concentrated sodium hydroxide solution added until no more oil separated. The aqueous layer was decanted and rejected. Saturated aqueous sodium iodide solution (6 ml.) was added to the residual oil, which was converted into a pink upper layer. After 1 hr. in a separator, the lower aqueous layer was run off and rejected. The oil was washed with aqueous sodium iodide solution (3 ml.), and the aqueous layer again rejected. After drying, the residue, which had partly solidified, was extracted with the minimum quantity of cool ethanol, the extract evaporated *in vacuo*, and the residue dried *in vacuo*, treated with 4-chloroquinaldine (1·95 g.) in methanol (7·5 ml.), and heated slowly to 160°, by which time the methanol had distilled off. The temperature of the bath was then kept at 160—170° for 1 hr. After cooling, the reddish-brown residue was triturated with a warm mixture of sodium iodide (15 g.), concentrated hydrochloric acid (7·5 ml.), and water (22·5 ml.). The mixture was then cooled and filtered (filtrate rejected), and the residue washed with water, sucked dry, dissolved in methanol (300 ml.), treated with sodium iodide (7·5 g.), refluxed for 10 min., then treated with charcoal and filtered. Ethanol (300 ml.) was added to the filtrate, and the mixture concentrated to 75 ml. Warm acetone (225 ml.) was added, the volume reduced to 75 ml., an equal volume of warm acetone added, and the mixture allowed to crystallise. The product was filtered off, washed with acetone–ethanol, then acetone and water, and dried. It was then dissolved in methanol (225 ml.), ethanol (225 ml.) added,

the solution concentrated to half-bulk, an equal volume of ethanol added, and the whole concentrated to 150 ml. and allowed to crystallise. The precipitate was filtered off, washed with ethanol, then with acetone, and dried, giving *4-amino-1-(6-4′-quinaldinylaminohexyl)quinaldinium iodide hydriodide* (4·3 g.), m. p. 288—289° (decomp.) (Found: C, 47·5; H, 4·95; N, 8·5; I, 38·7. $C_{26}H_{32}N_4I_2$ requires C, 47·7; H, 4·9; N, 8·6; I, 38·8%).

In a further experiment, crude 4-amino-*N*-6′-aminohexylquinaldinium iodide and 4-chloroquinaldine were refluxed in phenol for 1½ hr., then poured into acetone containing sodium iodide. The reaction was also carried out by using 4-methoxy-, 4-phenoxy-, 4-*o*-tolyloxy-, or 4-(2 : 4-xylyloxy)-quinaldine (in either phenol or *o*-cresol) in place of 4-chloroquinaldine. *4-o-Tolyloxyquinaldine* formed needles (from aqueous ethanol), m. p. 71—72° (Found: C, 81·2; H, 6·1; N, 5·85. $C_{17}H_{15}ON$ requires C, 81·9; H, 6·1; N, 5·6%) and *4-(2 : 4-xylyloxy)quinaldine*, needles (from aqueous alcohol), m. p. 86—87°, b. p. 138°/0·1 mm. (Found: C, 82·1; H, 6·5; N, 5·1. $C_{18}H_{17}ON$ requires C, 82·1; H, 6·5; N, 5·3%).

The following salts of " Substance II " were prepared: *Chloride hydrochloride* (from ethanol–acetone), m. p. 297—298° (decomp.) (Found: C, 66·1; H, 6·85; N, 11·8; Cl, 15·25. $C_{26}H_{32}N_4Cl_2$ requires C, 66·2; H, 6·85; N, 11·9; Cl, 15·1%). *Nitrate hydrogen nitrate* (from methanol–ethanol), m. p. 263—264° (decomp.) (Found: C, 59·2; H, 6·2; N, 16·15. $C_{26}H_{32}O_6N_6$ requires C, 59·5; H, 6·2; N, 16·0%). *Perchlorate hydrogen perchlorate* (from ethanol–methanol), m. p. 224—226° (decomp.) (Found: C, 52·2; H, 5·3; N, 9·2; Cl, 11·85. $C_{26}H_{32}O_8N_4Cl_2$ requires C, 52·1; H, 5·4; N, 9·35; Cl, 11·85%).

When an alcoholic solution of the iodide hydriodide was mixed with an aqueous solution of the sodium or ammonium derivatives of the following compounds, very sparingly soluble precipitates of the corresponding *salts* were obtained (these did not readily crystallise, and the analyses were determined on the freshly precipitated materials): 2 : 2′-dihydroxy-1 : 1′-dinaphthylmethane-3 : 3′-dicarboxylic acid, m. p. >300° (Found: C, 74·5; H, 6·1; N, 7·1. $C_{49}H_{46}O_8N_4$ requires C, 74·8; H, 5·9; N, 7·1%); 4 : 4′-diaminostilbene-2 : 2′-disulphonic acid, m. p. >300° (Found: N, 10·8; S, 7·9. $C_{40}H_{44}O_8N_6S_2$ requires N, 10·9; S, 8·3%); *Suramin*, sinters at 270° and slowly decomposes (Found: N, 10·0; S, 7·6. $C_{129}H_{136}O_{23}N_{18}S_6$ requires N, 10·1; S, 7·7%).

4-Amino-1-(ω-4′-quinaldinylaminoalkyl)quinaldinium iodides hydriodides were prepared as recorded in Table 3.

TABLE 3. *4-Amino-1-(ω-4′-quinaldinylaminoalkyl)quinaldinium iodides hydriodides.*

n in alkyl $[CH_2]_n$	Solvent *	M. p.†	Found (%)				Formula	Required (%)			
			C	H	N	I		C	H	N	I
4	M–E	311—312°	46·5	4·9	8·75	39·9	$C_{34}H_{38}N_4I_2$	46·0	4·5	8·95	40·6
5	,,	264—266	46·5	5·0	8·75	39·4	$C_{35}H_{40}N_4I_2$	46·9	4·7	8·75	39·7
7	E–A–Et	155—157	48·9	5·35	8·3	37·4	$C_{37}H_{44}N_4I_2$	48·5	5·1	8·4	38·0
8	E–A	251—253	49·35	5·4	8·2	36·9	$C_{38}H_{36}N_4I_2$	49·3	5·3	8·2	37·2
9	E–A–Et	190—192	49·8	5·45	7·6	35·8	$C_{39}H_{48}N_4I_2$	50·0	5·5	8·05	36·5
10	E–A	208—210	50·7	6·0	7·9	35·7	$C_{40}H_{40}N_4I_2$	50·7	5·7	7·9	35·8
14	E–A–Et	220—222	52·8	6·3	7·1	33·6	$C_{44}H_{48}N_4I_2$	53·3	6·3	7·3	33·2
16	,,	194—195	54·3	6·8	6·8	31·6	$C_{46}H_{52}N_4I_2$	54·4	6·6	7·05	32·0
18	M–A–Et	186—188	55·5	6·8	6·9	30·6	$C_{48}H_{56}N_4I_2$	55·5	6·9	6·8	30·9
20	E–A–Et	172—174	56·0	7·35	6·3	29·5	$C_{50}H_{60}N_4I_2$	56·5	7·1	6·6	29·9

* M = MeOH. E = EtOH. A = Acetone. Et = Et_2O. † With decomp.

Basification of " Substance II."—4-Amino-1-(6-4′-quinaldinylaminohexyl)quinaldinium iodide hydriodide (5 g.) was refluxed with potassium carbonate (5 g.) in methanol (200 ml.) and water (200 ml.) for 3 hr. on the steam-bath. Sodium iodide (50 g.) was then added, the mixture refluxed for a further 5 min., and the clear solution concentrated to half-bulk. An oil separated. Next morning the gum was filtered off, triturated several times with water, and dried, giving 4·4 g. of a friable mass. This was dissolved in ethanol (60 ml.) and after filtration concentrated to 20 ml.; warm acetone (40 ml.) was added. The following day the solvent was decanted from a small quantity of gum (which was rejected), an equal volume of acetone added, and the mixture set aside for several days with occasional scratching; crystals slowly separated. These were filtered off, washed with acetone, and recrystallised twice from ethanol–acetone, giving *4-amino-1-(6-4′-quinaldinylaminohexyl)quinaldinium iodide*, decomp. from 132—134° (Found: C, 59·2; H, 6·15; N, 10·5; I, 24·0. $C_{26}H_{31}N_4I$ requires C, 59·3; H, 5·9; N, 10·65; I, 24·1%).

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With alkyl halides this yielded the *methiodide* (from methanol–ethanol), m. p. 282—284° (decomp.) [mixed m. p. with the hydriodide, 265—270° (decomp.)] (Found: C, 48·2; H, 5·0; N, 8·3; I, 37·6. $C_{27}H_{34}N_4I_2$ requires C, 48·5; H, 5·1; N, 8·4; I, 38·0%), *ethiodide* (from methanol), m. p. 219—221° (decomp.) (Found: C, 48·9; H, 5·3; N, 8·1; I, 37·1. $C_{28}H_{36}N_4I_2$ requires C, 49·3; H, 5·3; N, 8·2; I, 37·2%), and *butiodide* (from ethanol–ether), m. p. 252—254° (decomp.) (Found: C, 50·2; H, 5·8; N, 8·2; I, 35·6. $C_{36}H_{46}N_4I_2$ requires C, 50·7; H, 5·7; N, 7·9; I, 35·8%).

When hexamethylenebis-(4-aminoquinaldinium iodide) (0·4 g.) was treated with potassium carbonate and sodium iodide in a similar manner it was recovered unchanged (0·38 g.).

We thank Dr. H. O. J. Collier for the pharmacological results, Dr. R. K. Callow of the National Institute of Medical Research, Mill Hill, for the infrared absorption spectra determinations, and the Directors of Allen and Hanburys Ltd. for permission to publish this work.

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[*Received, November 7th*, 1957.]

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299. *The Use of Adsorption for Isolation of Aromatic Substances.*

By A. ASATOOR and C. E. DALGLIESH.

The effect of competition between adsorbates during the isolation of aromatic substances by adsorption on, and desorption from, suitably deactivated charcoals has been examined. If adequate adsorbent is used, even minor components of complex mixtures can be isolated with good recoveries. The adsorption behaviour of some additional types of compound is reported.

THE study of metabolites in body fluids is simplified if a preliminary separation of given types of compound from the complex mixtures normally encountered is possible. Charcoal, suitably pre-treated, can be used [1,2] to isolate aromatic substances even in the presence of large excesses of inorganic or aliphatic substances. The pre-treatment, with long-chain aliphatic substances such as stearic acid or octadecylamine, blocks the most active adsorbing sites on the charcoal surface so that adsorption of aromatic substances on the remaining, less firmly-binding, sites is reversible and the adsorbed substances can be conveniently recovered by elution with aqueous phenol. This method applies to derivatives of benzene, pyrrole, pyridine, indole, purine, and pyrimidine, and depends on the presence of an aromatic ring in the adsorbate but, in general, not on the nature of other functional groups.[2] Bases are recovered in good yield by using a neutral eluant only if the charcoal has been pre-treated with a basic deactivating agent such as octadecylamine.

Body fluids may contain a wide variety of aromatic substances—normal human urine probably contains at least 100 phenols or derivatives of phenols, many in minute quantity. If adsorption is used for isolation, all the components of a mixture should in theory be recoverable provided that adsorption is reversible, and that an adequate amount of adsorbent is used to provide binding sites for all adsorbate molecules. Adsorption can be made very largely reversible by pre-treatment of the charcoals [2] and we now consider the effect of competition between adsorbates, and examine the applicability of the method to some other classes of compound.

Table 1 shows the effect of saligenin (*o*-hydroxybenzyl alcohol) on the adsorption and recovery of phenylalanine. With small amounts of saligenin the recovery of phenylalanine is unaffected, but as the amount of saligenin increases, increasing amounts of phenylalanine remain unadsorbed, with correspondingly poor recoveries. However if the amount of adsorbent is then increased a high recovery of phenylalanine can again be obtained even

[1] Dalgliesh, *J. Clin. Path.*, 1955, **8**, 73.
[2] Asatoor and Dalgliesh, *J.*, 1956, 2291.

in the presence of a three-hundredfold excess of saligenin. Similar results were obtained for the effect of varying amounts of *m*-hydroxybenzoic acid on the recovery of phenylalanine.

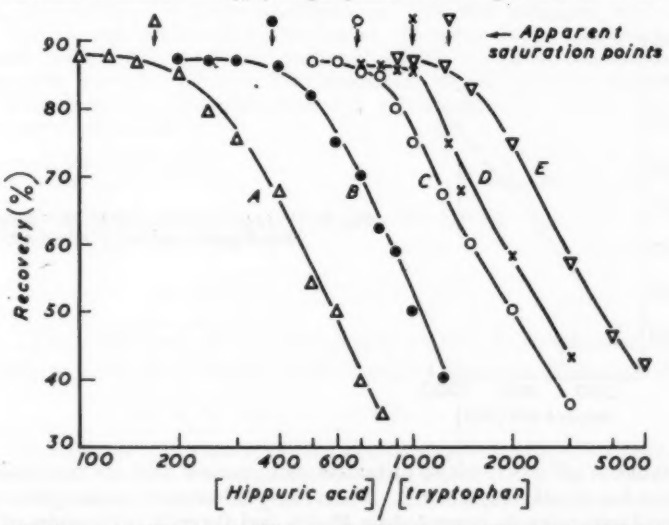
TABLE 1. *Adsorption behaviour of phenylalanine in the presence of saligenin.*

12·5 μmoles of phenylalanine were used in each case. The adsorbent was charcoal deactivated with 8% by weight of stearic acid, and the eluant was 50 ml. of 7% (w/v) of aqueous phenol/g. adsorbent.

Saligenin (μmoles)	Molar ratio of saligenin to phenylalanine	Adsorbent (g.)	Recovery of phenylalanine (%) Filtrate	Eluate	Saligenin (μmoles)	Molar ratio of saligenin to phenylalanine	Adsorbent (g.)	Recovery of phenylalanine (%) Filtrate	Eluate
20	1·6	1	3	94	4000	320	1	52	44
40	3·2	1	3	92	8000	640	1	73	26
80	6·4	1	3	92	8000	640	2	55	45
160	12·8	1	5	87	8000	640	4	21	73
400	32	1	13	81	4000	320	2	21	79
800	64	1	18	71	4000	320	3	10	84
1600	128	1	34	60	4000	320	3·5	5	89
3200	256	1	44	50	4000	320	4	5	89

Fig. 1 shows the effect of excess of hippuric acid on the recovery of tryptophan. For a given amount of adsorbent, recoveries of tryptophan are little affected by excess of hippuric acid until a point is reached, which we have called the "apparent saturation point", at

FIG. 1. *Recoveries (%) of 1 μmole of tryptophan in presence of excess of hippuric acid, varying amounts of charcoal deactivated with 8% by weight of stearic acid being used as adsorbent.*



Adsorbent: *A*, 125 mg.; *B*, 250 mg.; *C*, 500 mg.; *D*, 750 mg.; *E*, 1000 mg.

which presumably insufficient suitable adsorption sites remain available for binding all the tryptophan. Again, by increasing the amount of adsorbent good recoveries of tryptophan can be restored. The "apparent saturation points" in Fig. 1 are plotted against amount of adsorbent in Fig. 2. If adsorption were completely reversible this should give the straight (broken) line; the slight deviation which occurs shows a small degree of irreversible adsorption. However, from the practical aspect of recovering substances from solution, a very large excess of hippuric acid makes no appreciable difference to the recoverability of tryptophan from solution, provided adequate adsorbent is used. A similar set of curves was obtained for the recovery of anthranilic acid in the presence of excess of hippuric acid.

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The adsorption behaviour of various other substances is shown in Table 2. Pterins are well recovered; phenobarbitone (5-ethyl-5-phenylbarbituric acid), which contains a true aromatic ring, is also well recovered, but barbituric acid and quinalbarbitone [5-allyl-5-(1-methylbutyl)barbituric acid] are only partially recovered.

TABLE 2. *Adsorption behaviour of miscellaneous substances on charcoal deactivated with stearic acid.*

Substance	Molar concentration of adsorbate	Stearic acid used for deactivation (%)	Recovery Filtrate	Recovery Eluate
5-Hydroxyindolylacetic acid	0·0005	4	0	75
Xanthopterin	0·0005	4	0	86
*iso*Xanthopterin	0·00005	4	0	100
2 : 4 : 6-Trihydroxypteridine	0·005	4	0	97
	0·0005	4	0	100
Barbituric acid	0·005	8	3	41
	0·0005	8	2	44
Phenobarbitone	0·005	8	3	88
	0·0005	8	0	100
Quinalbarbitone	0·005	8	0	50
	0·0005	8	0	66

Under the standard conditions [2] histidine was largely unadsorbed. We therefore determined the adsorption behaviour of histidine, histamine, and urocanic acid at various pH values. Results obtained with stearic acid-deactivated charcoal are shown in Table 3. Results with octadecylamine-deactivated charcoal were similar. Maximal adsorption of

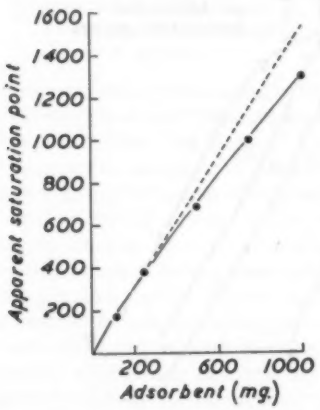

FIG. 2. *"Apparent saturation points" from Fig. 1 plotted against amount of adsorbent.*

histidine occurs at pH *ca.* 7, whilst histamine and urocanic acid are maximally adsorbed at alkaline and acid pH, respectively. Presumably adsorption occurs primarily through the uncharged molecules, as suggested by Phelps and Peters.[3] Recoveries of glyoxalines on elution with phenol are not satisfactory. However, histamine can be eluted almost quantitatively with phenol–hydrochloric acid.

We examined various substances as potential deactivating agents for charcoal, but none proved equal to stearic acid or octadecylamine. Those examined were surface-active agents, such as cetyltrimethylammonium bromide and sodium *p*-*n*-dodecyl- and -*n*-octylbenzenesulphonates, and aromatic substances such as anthracene, 1 : 5-dihydroxynaphthalene, 1 : 5-dihydroxyanthraquinone, and naphthalene-1 : 4 : 5 : 8-tetracarboxylic acid. In addition various substances were examined as potential eluants: these included aqueous solutions of benzyl alcohol, aniline, and pyridine and aqueous ethanolic solutions of

[3] Phelps and Peters, *Proc. Roy. Soc.*, 1929, *A*, **124**, 554.

6-methylheptyl alcohol, 1-methylheptyl alcohol, and *n*-hexyl alcohol; none was as effective as aqueous phenol.

TABLE 3. *Adsorption behaviour of glyoxalines at various* pH *values, charcoal deactivated with* 8% *by weight of stearic acid being used as adsorbent.*

Figures under filtrate and eluate represent percentage recoveries in appropriate fractions. 1 g. of adsorbent and 25 ml. of 0·005M-solutions of adsorbate were used. Elution was by 50 ml. of 7% (w/v) aqueous phenol.

pH for adsorption	Recovery of histidine		Recovery of histamine		Recovery of urocanic acid	
	Filtrate	Eluate	Filtrate	Eluate	Filtrate	Eluate
2·2	100	1	96	0	13	28
3·0	89	6	96	0	17	31
4·0	85	7	92	0	17	34
5·0	52	21	72	0	21	65
6·0	33	25	53	0	27	73
7·0	22	31	32	0	30	50
8·0	44	31	4	0	64	21
9·0	55	33	4	0	86	13
10·0	74	33	4	0	103	0

Experimental.—The preparation of adsorbents and the standard procedure for adsorption and elution have been described.[2] In experiments with glyoxalines McIlvaine buffer (Na_2HPO_4–citric acid) was used for pH 2·2—8, and Clark and Lubs buffer (H_3BO_3–KCl–NaOH) for pH 9 and 10. In the competition experiments the amount of the minor adsorbate was dissolved in sufficient aqueous solution (adjusted to pH 4 with acetic acid) to contain the appropriate amount of major adsorbate.

Methods of estimation. 5-Hydroxyindolylacetic acid was estimated with 1-nitroso-2-naphthol.[4] Pterins were estimated by ultraviolet absorption in 0·1N-sodium hydroxide at 255 mμ (xanthopterin), 340 mμ (*iso*xanthopterin), or 275 mμ (2 : 4 : 6-trihydroxypteridine). Barbiturates were estimated by ultraviolet absorption in pH 10 borate buffer at 257 mμ (barbituric acid) or 240 mμ (phenobarbitone and quinalbarbitone).[5] Other substances were estimated as previously described.[2]

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[*Received, November 29th,* 1957.]

[4] Udenfriend, Weissbach, and Clark, *J. Biol. Chem.*, 1955, **215**, 337.
[5] Goldbaum, *Analyt. Chem.*, 1952, **24**, 1604.

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300. *The Synthesis of* 2-O-β-D-*Xylopyranosyl*-L-*arabinose and its Isolation from the Partial Hydrolysis of Esparto Hemicellulose.*

By G. O. ASPINALL and R. J. FERRIER.

The structure of 2-*O*-β-D-xylopyranosyl-L-arabinose has been confirmed by a synthesis involving a Koenigs–Knorr condensation of 2 : 3 : 4-tri-*O*-acetyl-α-D-xylopyranosyl bromide with benzyl 3 : 4-*O*-*iso*propylidene-β-L-arabopyranoside, followed by removal of protecting groups. The disaccharide has also been identified as one of the products of partial acid hydrolysis of esparto hemicellulose.

THE disaccharide, 2-*O*-β-D-xylopyranosyl-L-arabinose, was first isolated as a product of partial acid hydrolysis of corn-cob hemicellulose B,[1,2] and the mode of linkage was established by methylation.[1] We have recently isolated the same compound from the partial acid hydrolysis of barley-husk hemicellulose.[3] Whistler and McGilvray [1] suggested that the positive rotation of the disaccharide was indicative of an α-D-xylopyranosyl

[1] Whistler and McGilvray, *J. Amer. Chem. Soc.*, 1955, **77**, 2212.
[2] Whistler and Corbett, *ibid.*, p. 3822.
[3] Aspinall and Ferrier, *J.*, 1957, 4188.

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linkage. Approximate calculations of the expected optical rotations of *O*-D-xylopyranosyl-L-arabopyranoses can be made by using Hudson's rule.[4] For example, the molecular rotation of *O*-β-D-xylopyranosyl-α-L-arabopyranose is given by the following expression, $[M]_D = B$(D-xylose) $- A$(methyl D-xylopyranoside) $+ B$(L-arabinose) $+ A$(L-arabinose). The Table shows the calculated optical rotations together with the observed physical constants for the known *O*-D-xylopyranosyl-L-arabinoses. Although the calculations do not take into account the relatively small differences likely to arise from linkages through different positions in the arabinose residue, the observed rotation for the 2-linked disaccharide is clearly consistent only with the presence of a β-D-xylopyranosyl linkage. Furthermore, the high optical rotation of 3-*O*-α-D-xylopyranosyl-L-arabinose, isolated from the partial acid hydrolysis of golden apple gum,[5] and of corn-fibre hemicellulose,[6] indicates that the two disaccharides probably have different configurations at the glycosidic linkage. We now report confirmation of the structure of the disaccharide by a synthesis of 2-*O*-β-D-xylopyranosyl-L-arabinose. Since the appearance of a preliminary account [7] of some of the following results, Charlson, Gorin, and Perlin [8] have proved the presence of a β-glycosidic link in the disaccharide by its degradation to 2-*O*-β-D-xylopyranosylglycerol.

Disaccharide	M. p.	$[\alpha]_D$	Source
2-*O*-β-D-Xylopyranosyl-L-arabinose (anhydrous form)	167—168°	+32·9°	Corn-cob hemicellulose B
monohydrate	80—81	+47·0° → +32·5°	—
trihydrate	97—99	+53·7° → +33·2°	Barley-husk hemicellulose
" " "	96—98	+55° → +31·5°	Synthesis
" " "	98—99	+49° → +30°	Esparto hemicellulose
3-*O*-α-D-Xylopyranosyl-L-arabinose	123	+173°	Golden apple gum
" " "	117·5—119	+166° → +181·8°	Corn-fibre hemicellulose
O-α-D-Xylopyranosyl-α-L-arabopyranose	—	+131° (calc.)	—
O-α-D-Xylopyranosyl-β-L-arabopyranose	—	+191° (calc.)	—
O-β-D-Xylopyranosyl-α-L-arabopyranose	—	+2° (calc.)	—
O-β-D-Xylopyranosyl-β-L-arabopyranose	—	+63° (calc.)	—

Since *O*-acyl-α-D-glycosyl halides with alcohols give the corresponding β-glycosides,[9] the required glycosidic bond of the disaccharide was formed by a Koenigs–Knorr condensation [10] of 2 : 3 : 4-tri-*O*-acetyl-α-D-xylopyranosyl bromide with benzyl 3 : 4-*O*-*iso*propylidene-β-L-arabopyranoside. The condensation product, benzyl 3 : 4-*O*-*iso*propylidene-2-*O*-(2 : 3 : 4-tri-*O*-acetyl-β-D-xylopyranosyl)-β-L-arabopyranoside, was isolated as a crystalline compound after chromatography on alumina; its deacetylation gave benzyl 3 : 4-*O*-*iso*propylidene-2-*O*-β-D-xylopyranosyl-β-L-arabopyranoside, which on hydrogenation (palladium–calcium carbonate) afforded 3 : 4-*O*-*iso*propylidene-2-*O*-β-D-xylopyranosyl-L-arabopyranose monohydrate. Mild acid hydrolysis of that monohydrate furnished the required disaccharide, which was readily separated from small amounts of xylose and arabinose and crystallised as 2-*O*-β-D-xylopyranosyl-L-arabinose trihydrate, identical (m. p. and mixed m. p., optical rotation, and *X*-ray single-crystal photograph) with the disaccharide previously isolated from the partial acid hydrolysis of barley-husk hemicellulose.[3]

A second crystalline condensation product (*A*) was isolated in low yield from the Koenigs–Knorr reaction. It is probable that this compound is a partially acetylated benzyl di-*O*-xylosylarabinose since hydrolysis gave xylose and arabinose in the proportion

[4] Hudson, *J. Amer. Chem. Soc.*, 1916, **38**, 1566.
[5] Andrews and Jones, *J.*, 1954, 4134.
[6] Whistler and Corbett, *J. Amer. Chem. Soc.*, 1955, **77**, 6328.
[7] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 819.
[8] Charlson, Gorin, and Perlin, *Canad. J. Chem.*, 1957, **35**, 365.
[9] Haynes and Newth, *Adv. Carbohydrate Chem.*, 1955, **10**, 207.
[10] Koenigs and Knorr, *Ber.*, 1901, **34**, 957.

of 1·8 to 1, and since the infrared spectrum contained a sharp absorption at 3531 cm.$^{-1}$ showing the presence of a single hydroxyl group in the molecule. The product (*B*) of deacetylation consumed 4·4 mol. of periodate, slightly more than the expected 4 mol. Methylation and deacetylation of material *A* gave a methylated trisaccharide, whose hydrolysis gave 2 : 3 : 4-tri-*O*-methylxylose and a mono-*O*-methylarabinose. The latter was shown to be the 2-methyl ether since chromatography of the products of periodate oxidation [11] showed methoxymalondialdehyde and since the derived mixture of methyl pyranosides was attacked by periodate. Although insufficient of the trisaccharide derivative (*A*) was available for a complete characterisation, these experiments suggest that compound *B* is benzyl 3 : 4-di-*O*-β-D-xylopyranosyl-β-L-arabopyranoside and that material *A* is a partially acetylated derivative. Although there is no apparent reason for the instability of benzyl 3 : 4-*O*-*iso*propylidene-β-L-arabopyranoside during the Koenigs–Knorr reaction, it is clear that some hydrolysis of the *iso*propylidene group took place since benzyl β-L-arabopyranoside was also isolated from the mixture. The trisaccharide derivative (*A*) must have been formed by condensation of tri-*O*-acetyl-α-D-xylopyranosyl bromide with benzyl β-L-arabopyranoside.

During the isolation of xylobiose and xylotriose from the partial acid hydrolysis of esparto hemicellulose,[12] a small fraction was obtained which contained xylobiose and a second disaccharide having the same chromatographic mobility as 2-*O*-β-D-xylopyranosyl-L-arabinose.* This compound was separated chromatographically and was isolated as the crystalline 2-*O*-β-D-xylopyranosyl-L-arabinose trihydrate. It is clear that this disaccharide arises from a hitherto unrecognised structural feature of esparto hemicellulose. Previous investigations have shown that esparto hemicellulose contains at least two xylans, one [13] devoid of and one [14] containing arabinose residues, the majority of which are present as end groups in the furanose form. The structural significance of the isolation of 2-*O*-β-D-xylopyranosyl-L-arabinose from esparto hemicellulose is not yet clear. It may be recalled, however, that a small quantity of an unidentified di-*O*-methylarabinose was isolated from the hydrolysis of methylated esparto araboxylan;[14] the optical rotation and chromatographic mobility of this sugar were similar to those of 3 : 5-di-*O*-methyl-L-arabinose. 1 : 2-Linked L-arabofuranose residues would be present in esparto hemicellulose if 2-*O*-β-D-xylopyranosyl-L-arabofuranosyl side-chains were attached to the backbone of 1 : 4-linked β-D-xylopyranose residues as in barley-husk hemicellulose.[3]

Experimental

Alumina, Type H, 100/200 S mesh, supplied by Peter Spence and Sons, Ltd., was shaken with N-acetic acid, washed with water by decantation until free from acid, and dried at 260°. Optical rotations were observed at 18° ± 2°.

Benzyl 3 : 4-O-iso*propylidene*-β-L-*arabopyranoside*.—Benzyl β-L-arabopyranoside (20 g.) in acetone (1 l.) was shaken with cupric sulphate (60 g.) and concentrated sulphuric acid (1 ml.) for 24 hr. The acetone solution was separated, acid was neutralised by passing in dry ammonia, salts were removed by filtration, and the solution was concentrated to a syrup. The syrup was extracted with ether and the extract (23 g.) was redissolved in ether and chromatographed on alumina (25 × 5 cm.). Elution with ether containing 5% ethanol, followed by two recrystallisations from light petroleum (b. p. 60—80°)–ether (3 : 1), afforded *benzyl* 3 : 4-O-iso*propylidene*-β-L-*arabopyranoside* (10 g.), m. p. 57—58°, $[\alpha]_D$ +187° (*c* 0·9 in $CHCl_3$) (Found: C, 64·7; H, 7·2. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·2%). Ballou [15] reports m. p. 55—58°, $[\alpha]_D$ −208° (EtOH), for benzyl 3 : 4-*O*-*iso*propylidene-β-D-arabopyranoside.

Condensation of 2 : 3 : 4-*Tri*-O-*acetyl*-α-D-*xylopyranosyl Bromide and Benzyl* 3 : 4-O-iso*propylidene*-β-L-*arabopyranoside*.—Benzyl 3 : 4-*O*-*iso*propylidene-β-L-arabopyranoside (9·2 g.), freshly

* We are grateful to Dr. Mary E. Carter for drawing our attention to the presence of this disaccharide.

[11] Lemieux and Bauer, *Canad. J. Chem.*, 1953, **31**, 814.
[12] Aspinall, Carter, and Los, *J.*, 1956, 4807.
[13] Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289.
[14] Aspinall, Hirst, Moody, and Percival, *J.*, 1953, 1631.
[15] Ballou, *J. Amer. Chem. Soc.*, 1957, **79**, 165.

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prepared silver carbonate (15 g.), and anhydrous calcium sulphate (40 g.) were shaken overnight in benzene (100 ml.). After addition of iodine (3 g.), a solution of 2 : 3 : 4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (11·1 g.) in benzene (100 ml.) was added slowly with stirring during 1 hr. The mixture was shaken in the dark for 3 days (with occasional release of carbon dioxide); the benzene solution then gave no opalescence with ethanolic silver nitrate. Filtration of the mixture followed by concentration of the filtrate yielded a syrup (16 g.), which was chromatographed in benzene on alumina (25 × 5 cm.) to give 6 fractions.

Fraction 1. The solid [1·8 g.; eluted with light petroleum–benzene (1 : 1)] after two recrystallisations from light petroleum containing a little ethanol gave *benzyl* 3 : 4-O-*isopropylidene*-2-O-(2 : 3 : 4-*tri*-O-*acetyl*-β-D-*xylopyranosyl*)-β-L-*arabopyranoside* (1·35 g.), m. p. 110—111°, $[\alpha]_D$ +71° (*c* 1·0 in $CHCl_3$), $[\alpha]_D$ +78° (*c* 1·0 in MeOH) (Found: C, 58·3; H, 6·4. $C_{26}H_{34}O_{12}$ requires C, 58·0; H, 6·4%).

Fraction 2. The syrup [0·6 g.; eluted with light petroleum–benzene (1 : 3)] was dissolved in ethanol, crystals were deposited, and recrystallisation from ethanol gave compound *A* (200 mg.), m. p. 154—155°, $[\alpha]_D$ +38° (*c* 1·0 in $CHCl_3$). Hydrolysis of a sample of *A* gave xylose and arabinose in the ratio of 1·8 : 1 (quantitative chromatography [16]). Deacetylation of *A* with sodium methoxide gave compound *B*, which after recrystallisation from ethanol–water had m. p. 261—263° [Found: C, 52·0; H, 6·3. Benzyl di-*O*-β-D-xylopyranosyl-β-L-arabopyranoside ($C_{23}H_{32}O_{13}$) requires C, 52·4; H, 6·3%)]. The benzyl glycoside *B* consumed 4·4 mol. of periodate (spectrophotometric determination [17]). Direct methylation of *A* with methyl sulphate and sodium hydroxide and hydrolysis of the methylated trisaccharide gave two components *a* and *b*, R_G 0·95 (cf. 2 : 3 : 4-tri-*O*-methyl-D-xylose) and 0·37 in butan-1-ol–ethanol–water (4 : 1 : 5; upper layer). Chromatography [11] of the product of the periodate oxidation of *b* showed methoxymalondialdehyde. Demethylation of *b* with hydrobromic acid gave arabinose. The derived syrup of methyl pyranosides consumed *ca.* 1 mol. of periodate.

Fractions 3 *and* 4. Benzyl β-L-arabopyranoside, m. p. and mixed m. p. 172—173°, was deposited from ethanolic solutions of fractions 3 (2·1 g.; eluted with benzene) and 4 [1·6 g.; eluted with benzene–ether (1 : 1)].

Fraction 5. The syrup [2·1 g.; eluted with ether–ethanol (1 : 1)] was dissolved in ethanol; crystals were deposited, m. p. 141—142°, $[\alpha]_D$ +69° (*c* 1·3 in $CHCl_3$) {cf. 2 : 3 : 4-tri-*O*-acetyl-D-xylose, m. p. 138—141°, $[\alpha]_D$ +70° ($CHCl_3$) [18]}.

Fraction 6. The mobile oil (3·6 g.; eluted with acetone), $[\alpha]_D$ +10° (*c* 1·2 in H_2O), when hydrolysed, gave approximately equal amounts of xylose and arabinose.

Benzyl 3 : 4-O-iso*propylidene*-2-O-β-D-*xylopyranosyl*-β-L-*arabopyranoside*.—Methanolic 0·1N-sodium methoxide (6 ml.) was added to benzyl 3 : 4-*O*-*iso*propylidene-2-*O*-(2 : 3 : 4-tri-*O*-acetyl-β-D-xylopyranosyl)-β-L-arabopyranoside (1·20 g.) in methanol (60 ml.), and after the mixture had been shaken for 6 hr. crystals separated. Recrystallisation from methanol afforded *benzyl* 3 : 4-O-iso*propylidene*-2-O-β-D-*xylopyranosyl*-β-L-*arabopyranoside* (0·75 g.), m. p. 216—217°, $[\alpha]_D$ +132° (*c* 0·5 in MeOH) (Found: C, 58·2; H, 6·6. $C_{26}H_{36}O_9$ requires C, 58·3; H, 6·8%).

2-O-β-D-*Xylopyranosyl*-L-*arabinose*.—The above benzyl glycoside (0·72 g.) in ethanol–water (100 ml.) was shaken in hydrogen at atmospheric pressure in the presence of palladium hydroxide (5%)–calcium carbonate (4 g.) for 6 hr. Catalyst was filtered off and the filtrate concentrated to a syrup (0·55 g.). Extraction of the product with boiling acetone, followed by removal of solvent, afforded a crystalline *compound* (0·50 g.), m. p. 141—143°, $[\alpha]_D$ +53° (equil.) (*c* 0·7 in H_2O). Although no satisfactory solvent could be found for recrystallisation, this substance was probably 3 : 4-*O*-*iso*propylidene-2-*O*-β-D-xylopyranosyl-L-arabinose monohydrate (Found: C, 45·3; H, 7·0. $C_{13}H_{22}O_9.H_2O$ requires C, 45·9; H, 7·1%). This substance (0·28 g.) was heated at 100° for 40 min. with 0·005N-oxalic acid (10 ml.), the solution was neutralised with Amberlite resin IR-4B(OH), and the filtrate was concentrated to a syrup (0·20 g.). Recrystallisation from ethanol–water furnished 2-*O*-β-D-xylopyranosyl-L-arabinose trihydrate (120 mg.), which had m. p. and mixed m. p. 96—98°, $[\alpha]_D$ +55° (3 min.) ⟶ +31·5° (90 min., const.) (*c* 1·5 in H_2O), and gave an *X*-ray single-crystal photograph identical with that of an authentic sample.

Isolation of 2-O-β-D-*Xylopyranosyl*-L-*arabinose from the Partial Hydrolysis of Esparto Hemicellulose*.—During the isolation of xylobiose and xylotriose from the partial acid hydrolysis of esparto hemicellulose,[12] a small fraction (350 mg.) was obtained from the fractionation on

[16] Flood, Hirst, and Jones, *J.*, 1948, 1679.
[17] Aspinall and Ferrier, *Chem. and Ind.*, 1957, 1216.
[18] Hudson and Dale, *J. Amer. Chem. Soc.*, 1918, **40**, 997.

charcoal–celite which was shown by paper chromatography in ethyl acetate–pyridine–water (10 : 4 : 3) to contain two components, xylobiose and an unidentified sugar, having R_{xylose} 0·59 and 0·67. The sugars were separated chromatographically on filter sheets and the faster-moving component (50 mg.) crystallised from ethanol–water to give 2-*O*-β-D-xylopyranosyl-L-arabinose trihydrate (20 mg.), m. p. 98—99°, $[\alpha]_D$ +49° (3 min.) ⟶ +30° (1 hr., const.) (*c* 1·0 in H_2O). The sugar was chromatographically indistinguishable in three solvent systems from the authentic disaccharide, hydrolysis gave xylose and arabinose, and hydrolysis of the derived aldobionic acid (bromine oxidation) gave only xylose. An *X*-ray single-crystal photograph was identical with that of the disaccharide isolated from barley-husk hemicellulose.[3]

The authors thank Professor E. L. Hirst, F.R.S., for his interest and advice. This work was carried out under the auspices of the Brewing Industry Research Foundation, to whom the authors are indebted for the award of a scholarship to one of them (R. J. F.).

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301. *Raman Spectrum and Constitution of Fused Gallium Dibromide.*

By L. A. WOODWARD, N. N. GREENWOOD, J. R. HALL, and I. J. WORRALL.

Gallium dibromide was prepared as a white crystalline compound, m. p. 166·7°. Its Raman spectrum in the fused state at approx. 180° was in close agreement with that previously found for the $GaBr_4^-$ ion in aqueous solution. In the fused state, therefore, gallium dibromide is to be formulated as $Ga^+[GaBr_4]^-$. This conclusion is supported by the electrical conductivity of the melt, and is also consistent with the observed diamagnetism of the solid.

THE structure of gallium dibromide is of interest since the empirical formula $GaBr_2$ appears to indicate a valency of 2 for gallium, whereas the normal valency of Group III elements is 3 or 1. Very little is to be found in the literature about the compound. The original preparation of gallium dibromide has been attributed [1] to Lecoq de Boisbaudran; but although in 1878 he briefly announced the preparation of several anhydrous halides of gallium [2] and subsequently distinguished the dichloride [3] from the trichloride, his publications do not appear to contain any reference to the dibromide. The first evidence for the existence of a lower bromide seems to have been given in 1930 by Johnson and Parsons,[4] who reported a relatively involatile residue in their tribromide preparation. The promised paper describing the properties of the lower bromide has never appeared. The dibromide was mentioned in 1932 by Klemm and Tilk,[5] but again the promised further report has not appeared. In 1934 Miescher and Wehrli [6] described briefly the preparation of a compound, stated to be the dibromide, by a method analogous to that used for the dichloride, *i.e.*, by reduction of the tribromide with excess of gallium metal. As far as we are aware, no subsequent publication on the compound has appeared; but we are informed by Mr. F. M. Brewer that it has been prepared in Oxford a number of times by his collaborators,[7] who have studied some of its properties and in particular shown it to have the empirical formula $GaBr_2$.

[1] Gmelin-Kraut, "Handbuch der anorganischen Chemie," Winter, Heidelberg, 1911, Vol. 4, 1, p. 214; Mellor, "Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green and Co., London, 1925, Vol. 5, p. 384.
[2] Lecoq de Boisbaudran and Jungfleisch, *Compt. rend.*, 1878, **86**, 577; Lecoq de Boisbaudran, *ibid.*, p. 756.
[3] Lecoq de Boisbaudran, *ibid.*, 1881, **93**, 294.
[4] Johnson and Parsons, *J. Phys. Chem.*, 1930, **34**, 1210.
[5] Klemm and Tilk, *Z. anorg. Chem.*, 1932, **207**, 161.
[6] Miescher and Wehrli, *Helv. Phys. Acta*, 1934, **7**, 331.
[7] Spencer-Palmer, Chemistry Part II Thesis, Oxford, 1941; Garton, D.Phil. Thesis, Oxford, 1953.

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No investigation of the structure of gallium dibromide has been reported. If the molecular formula were $GaBr_2$, the compound would be paramagnetic. Analogy with the dichloride suggests, however, that it will have the formula Ga_2Br_4 and be diamagnetic. As with the dichloride, the question then arises as to whether the structure is of the covalent type $Br_2Ga–GaBr_2$, involving a bond between two gallium atoms, or of the ionic type $Ga^+[GaBr_4]^-$, in which the apparent valency of 2 is due to the univalency of one of the gallium atoms and the tervalency of the other.

A recent study of the Raman spectrum of fused gallium dichloride [8] has decided in favour of the ionic structure for that compound. The present paper reports similar work for the dibromide.

Results and Discussion.—The Raman spectrum of gallium dibromide in the fused state at approx. 180° (*i.e.*, approx. 13° above its m. p.) consisted of four frequencies and is described in Table 1, which gives observed frequency shifts together with estimated intensities, appearances, and states of polarisation of the lines. For comparison, Table 2

TABLE 1. *Raman spectrum of fused gallium dibromide.*

$\Delta\nu$ (cm.$^{-1}$)	79	107	209	288
Intensity	Strong	Strong	Very strong	Weak
Appearance	Sharp	Sharp	Sharp	Diffuse
Polarisation	Depolarised	Depolarised	Strongly polarised	Depolarised

reproduces the spectrum obtained by Woodward and Nord [9] for the tetrabromogallate ion, $GaBr_4^-$, in an aqueous solution of gallium tribromide containing excess of hydrobromic acid. The number of lines and their states of polarisation prove that the ion is a regular tetrahedron (point-group T_d). The appropriate assignments are included in Table 2. The very close similarity of the two spectra is obvious, and the case is thus

TABLE 2. *Raman spectrum of the* $GaBr_4^-$ *ion in aqueous solution.*

$\Delta\nu$ (cm.$^{-1}$)	71	102	210	278
Intensity	Strong	Strong	Very strong	Rather weak
Appearance	Sharp	Sharp	Sharp	Diffuse
Polarisation	Depolarised	Depolarised	Strongly polarised	Depolarised
Assignment	$\nu_2(E)$	$\nu_4(F_2)$	$\nu_1(A_1)$	$\nu_3(F_2)$

analogous to that of the fused dichloride.[8] Within the estimated limits of error of the measured $\Delta\nu$ values, the frequency ν_1 of the most intense, strongly polarised line is practically identical in Tables 1 and 2. Each of the two lower frequencies of the dibromide also agrees closely with the corresponding frequency of the tetrabromogallate ion. The highest frequency appears in both spectra as a diffuse Raman line (breadth approx. 35 cm.$^{-1}$) whose centre (as given in Tables 1 and 2) is difficult to locate precisely; but here also the difference between the two spectra is not large.

These findings prove that fused gallium dibromide contains $GaBr_4^-$ ions as the predominant polyatomic species. The close agreement between the spectra is remarkable in view of the considerable difference to be expected between the interactions in molten gallium dibromide on the one hand and aqueous solution at room temperature on the other. We conclude that the vibrational frequencies of the tetrabromogallate ion (like those of the tetrachlorogallate ion [8]) are insensitive to environmental changes. As discussed at greater length for fused gallium dichloride,[8] the observed spectrum is not consistent with the presence of $Br_2Ga–GaBr_2$ molecules or any ionic species derivable therefrom by the dissociation of bromide ions. Therefore, the melt is to be formulated as gallium(I) tetrabromogallate(III), $Ga^+[GaBr_4]^-$.

This conclusion is supported by other measurements. First, experiment showed that

[8] Woodward, Garton, and Roberts, *J.*, 1956, 3723.
[9] Woodward and Nord, *J.*, 1955, 2655.

(like the dichloride [10]) the solid dibromide at room temperature is diamagnetic, which rules out the molecular formula $GaBr_2$. Secondly, the electrical conductivity of the melt is close to that of many fused salts, especially those in which the cation is considerably smaller than the anion. Table 3 gives the values of the specific conductivity κ, the molar conductivity μ, and the reduced conductivity $\mu\eta$ (where η is the dynamic viscosity) for fused gallium dibromide at its m. p. 166·7°. For comparison, Table 3 includes corresponding data [11] for fused silver nitrate at about 11° above its m. p. The values of the specific conductivity for the two compounds are of the same order of magnitude; the

TABLE 3. *Electrical conductivity of fused gallium dibromide.*

	Temp.	κ (ohm^{-1} cm.$^{-1}$)	μ (ohm^{-1} cm.^{2} mole^{-1})	$\mu\eta$ (ohm^{-1} cm.^{2} mole^{-1} cP.)
Fused $Ga^+GaBr_4^-$	166·7°	0·1491	19·73	136·4
Fused $Ag^+NO_3^-$	220	0·693	29·8	135

molar conductivities are more nearly equal; and when allowance for viscosity is made, the reduced conductivities are practically identical. That the melt is ionic is thus supported by the electrical conductivity.

EXPERIMENTAL

Preparation and Purification of Gallium Dibromide.—Gallium tribromide [12] was heated at 180° in a sealed evacuated tube with slightly less than the theoretical weight of gallium metal. When all the gallium had dissolved, most of the excess of tribromide was sublimed from the mixture by cooling one end of the reaction tube in a blast of air. During this sublimation, which required several days, the m. p. of the mixture rose from 150° to 158°. Further purification was by fractional crystallisation of the melt, one-fifth of the sample being discarded in each cycle. The first crystallisation raised the m. p. to 164°, and after five more cycles it had become constant at 166·7°. The solid was colourless.

It is not feasible to prepare pure gallium dibromide by heating the tribromide with excess of gallium metal [6] and subliming the product in a vacuum, for the dibromide slowly disproportionates above 200°.

Determination of Physical Properties.—The dibromide was repurified before each experiment by fractional freezing in a vessel attached directly to the measuring apparatus (conductivity cell, viscometer, etc.) which was finally sealed off without breaking the vacuum.[13]

Raman Spectrum.—The apparatus (Toronto arc excitation, Hilger E 518 spectropraph) has been described.[14] The purified gallium dibromide was transferred to the Raman vessel *in vacuo*. During the exposures it was kept molten at approx. 180° by a stream of electrically preheated air passing through the annular space between the Raman vessel and the surrounding Dewar sleeve. The molten sample was clear and pale straw-yellow. It was nevertheless possible to observe the Raman spectrum excited by the blue mercury line 4358 Å and the violet line 4046 Å. Indeed, the scattering was found to be intense. By using Kodak special scientific plates (type Oa, sensitivity G) the complete Raman spectrum from the blue line 4358 Å could be photographed with an exposure time of only 5 min. Longer times revealed no new features. A slight continuum appeared in the region between Hg 4358 Å and Hg 4916 Å, which might have tended to mask weak Raman lines with the longer exposures. However, this continuum (presumably due to a trace of fluorescence) was almost completely suppressed by using as filter an aqueous solution of sodium nitrite or, better, a benzene solution of *m*-dinitrobenzene. There was no sign of deterioration of the sample as a result of the repeated melting and irradiation.

Qualitative determinations of the states of polarisation of the Raman lines were made by the method of polarised incident light, oriented polaroid cylinders surrounding the Raman tube. Frequencies were measured in the usual manner with a copper-arc spectrum as standard. The

[10] Klemm and Tilk, *Z. anorg. Chem.*, 1932, **207**, 175.
[11] Landolt and Börnstein, "Physikalisch-chemische Tabellen," 5th edn., Berlin, 1923. More recent determinations are in substantial agreement.
[12] Greenwood and Worrall, *J. Inorg. Nucl. Chem.*, 1957, **3**, 357.
[13] Greenwood and Wade, *J.*, 1957, 1516; *J. Inorg. Nucl. Chem.*, 1957, **3**, 349.
[14] Rolfe and Woodward, *Trans. Faraday Soc.*, 1954, **50**, 1030; Woodward and Roberts, *J.*, 1956, 1170.

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estimated limits of error of the $\Delta\nu$ values are about ± 2 cm.$^{-1}$ for the strong sharp lines. The value given in Table 1 for the highest frequency, which appeared as a diffuse line, refers to the estimated centre and may be subject to a larger error.

We are indebted to the Royal Society for a grant (to L. A. W.) with which the spectrograph was bought, and to the Chemical Society for a grant (to N. N. G.) for the purchase of gallium. We also thank the University of Queensland for a Research Scholarship (to J. R. H.) and the University of Nottingham for a Research Scholarship (to I. J. W.).

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[*Received, November 18th*, 1957.]

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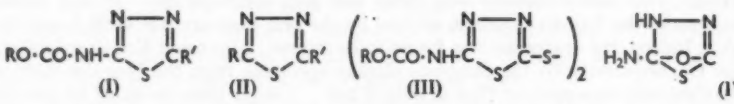
302. *Preparation and Hydrolysis of Some Derivatives of 1 : 3 : 4-Thiadiazole.*

By V. PETROW, O. STEPHENSON, A. J. THOMAS, and A. M. WILD.

Some 5-alkoxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonamides have been prepared and their reactions and those of certain intermediates studied.

OUR object was the preparation of a series of 5-alkoxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonamides (I; R = alkyl, R′ = $SO_2{\cdot}NH_2$) for study as carbonic anhydrase inhibitors.[1]

2-Amino-5-mercapto-1 : 3 : 4-thiadiazole (II; R = NH_2, R′ = SH), required as starting material, was originally prepared by Guha [2] by heating ethanolic potassium thiosemicarbazidedithiocarboxylate under pressure. We find that this thiadiazole is formed in excellent yield when thiosemicarbazide is heated with carbon disulphide and an equivalent of potassium hydroxide, or with ethyl potassium xanthate in ethanol or ethylene glycol. A small quantity of 2 : 5-dimercapto-1 : 3 : 4-thiadiazole (II; R = R′ = SH) is formed as by-product, presumably by hydrolysis of the thiosemicarbazide to hydrazine and reaction of the latter with carbon disulphide. Conversion of the amino-thiol (II; R = NH_2, R′ = SH) into the alkoxycarbonylamino-thiols (I; R = alkyl, R′ = SH) was effected by reaction with the alkyl chloroformate in pyridine: with excess of the chloroformate, disubstitution products (I; R = alkyl, R′ = $S{\cdot}CO_2R$) were formed, but with the exception of the benzyl derivative these passed into the alkoxycarbonyl-amino-thiols on crystallisation from ethanol or aqueous ethanol.



Conversion of the alkoxycarbonylamino-thiols (I; R = alkyl, R′ = SH), and also of the foregoing dibenzyl derivative, into the corresponding sulphonyl chlorides (R′ = SO_2Cl) was readily achieved by chlorination under fairly critical conditions (cf. refs. 1, 3, 4). Chlorination of the *n*-hexyl derivative (I; R = C_6H_{13}, R′ = SH) in 70% acetic acid at 0—5° gave the sulphonyl chloride and a small quantity of the disulphide (III; R = C_6H_{13}). Use of 50% acetic acid at −2° to 0° led to the formation of the disulphide which, however, was converted into the sulphonyl chloride by chlorine in 70% acetic acid at 15°. In anhydrous dioxan at 10°, only the chloro-derivative (I; R = C_6H_{13}, R′ = Cl)

[1] Roblin and Clapp, *J. Amer. Chem. Soc.*, 1950, **72**, 4890; Miller, Dessert, and Roblin, *ibid.*, p. 4893.
[2] Guha, *ibid.*, 1922, **44**, 1510.
[3] Schiller and Otto, *Ber.*, 1876, **9**, 1638; Zincke and Frohneberg, *Ber.*, 1909, **42**, 2728; Douglass and Johnson, *J. Amer. Chem. Soc.*, 1938, **60**, 1486; Lee and Dougherty, *J. Org. Chem.*, 1940, **5**, 81.
[4] Findlay and Dougherty, *J. Amer. Chem. Soc.*, 1946, **68**, 1666.

was obtained (cf. Findlay and Dougherty [4]). The sulphonyl chloride was also prepared by reaction of the thiol with iodobenzene dichloride or with *tert.*-butyl hypochlorite, the latter reagent yielding products essentially free from the disulphide. With sodium hypochlorite in alkaline solution or with chlorine in alkaline *tert.*-butyl alcohol the thiol yielded the disulphide as the major product. Incidentally, the pure sulphonyl chlorides slowly decomposed at room temperature with evolution of sulphur dioxide, and rapidly at their melting points, the nuclear chloro-compounds (I; R = alkyl, R′ = Cl) being obtained in almost theoretical yields.

The sulphonyl chlorides were converted smoothly into the required sulphonamides (I; R′ = $SO_2 \cdot NH_2$) by aqueous or liquid ammonia or by suspensions of ammonium carbonate or hydrogen carbonate in benzene. Hydrazine removed the sulphonyl group from the sulphonyl chloride (I; R = C_6H_{13}, R′ = SO_2Cl) with formation of 2-*n*-hexyloxycarbonylamino-1 : 3 : 4-thiadiazole (I; R = C_6H_{13}, R′ = H).

The *n*-hexyloxy-amide (I; R = C_6H_{13}, R′ = $SO_2 \cdot NH_2$) was stable in aqueous-ethanolic N-hydrochloric acid, but was converted by 4N-acid into the 5-hydroxy-derivative (I; R = C_6H_{13}, R′ = OH), also obtained from the corresponding sulphonamide and sulphonyl chloride by treatment with acetic anhydride. 5-Acetamido-1 : 3 : 4-thiadiazole-2-sulphonamide (" Diamox ") (II; R = NHAc, R′ = $SO_2 \cdot NH_2$) behaved differently with 4N-hydrochloric acid, being converted into the amine hydrochloride (II; R = NH_2Cl, R′ = $SO_2 \cdot NH_2$). In acetic anhydride it passed into the hydroxy-derivative (II; R = NHAc, R′ = OH), also formed in low yield when 1-phenyl-5-thiodiurea ($Ph \cdot NH \cdot CO \cdot NH \cdot NH \cdot CS \cdot NH_2$) was subjected to short treatment with the same reagent,[5] and it was hydrolysed to 2-amino-5-hydroxy-1 : 3 : 4-thiadiazole (II; R = NH_2, R′ = OH).

2-Amino-5-hydroxy-1 : 3 : 4-thiadiazole of m. p. 177° was prepared by Freund and Schander [6] by heating 2-thiodiurea ($NH_2 \cdot CO \cdot NH \cdot NH \cdot CS \cdot NH_2$) with concentrated hydrochloric acid but Guha used acetic anhydride for the cyclisation, obtaining an acetyl derivative which gave a base, m. p. 235°, apparently isomeric with Freund and Schander's material. Its structure was investigated by Janniah and Guha [8] who converted the base of m. p. 177° into an acetyl derivative which gave the product, m. p. 235°, on hydrolysis. The last compound was insoluble in alkali and did not react with mercuric chloride, but formed derivatives with phenyl *iso*cyanate and *iso*thiocyanate and with benzaldehyde, on which basis it was assigned the constitution (IV).

Attempts to repeat Freund and Schander's preparation surprisingly proved unsuccessful, but there seems little doubt that their product is authentic 2-amino-5-hydroxy-1 : 3 : 4-thiadiazole, which we have additionally obtained by the action of acetic anhydride on 1-ethoxycarbonylthiosemicarbazide.[9] Guha's base of m. p. 235°, in contrast, is formulated by us as 2-amino-5-methyl-1 : 3 : 4-thiadiazole (II; R = NH_2, R′ = Me). Reaction of 2-thiobiurea with formic acid and with propionic anhydride similarly yielded 2-amino-1 : 3 : 4-thiadiazole (II; R = NH_2, R′ = H) and its 5-ethyl homologue (R′ = Et), respectively.

Experimental

Ultraviolet absorptions refer to EtOH solutions unless otherwise stated.

2-Amino-5-mercapto-1 : 3 : 4-thiadiazole (II; R = NH_2, R′ = SH).—To thiosemicarbazide (182 g.) suspended in anhydrous ethanol (700 ml.) were added anhydrous sodium carbonate (106 g.) and carbon disulphide (184 g.). The mixture was warmed with stirring under reflux for 1 hr., then heated on the steam-bath for 4 hr. The solvent was largely removed, and the residue dissolved in water (800 ml.) and just acidified with concentrated hydrochloric acid (*ca.* 160 ml.) to give the product (216 g.), m. p. 232° (decomp.).

[5] Cf. Guha and Chakraborty, *J. Indian Chem. Soc.*, 1929, **6**, 99.
[6] Freund and Schander, *Ber.*, 1896, **29**, 2506.
[7] Guha, *J. Amer. Chem. Soc.*, 1923, **45**, 1036.
[8] Janniah and Guha, *ibid.*, 1930, **52**, 4860; *J. Indian Inst. Sci.*, 1933, *A*, **16**, 19.
[9] Fromm and Nehring, *Ber.*, 1923, **56**, 1374.

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2-Alkoxycarbonylamino-5-mercapto-1 : 3 : 4-thiadiazole.—The preparative method is exemplified as follows: 2-Amino-5-mercapto-1 : 3 : 4-thiadiazole (66·5 g.) in pyridine (180 ml.) was stirred and treated dropwise below 40° with ethyl chloroformate (55·2 g.) during 1 hr. The mixture was diluted, then acidified with hydrochloric acid with cooling, and the *product* collected and crystallised from water (see Table 1).

Preparation of Sulphonyl Chlorides (I; R′ = SO_2Cl).—The preparative method is exemplified as follows: Finely powdered 2-ethoxycarbonylamino-5-mercapto-1 : 3 : 4-thiadiazole (50 g.) in 70% acetic acid (600 ml.) was treated with stirring at 0—5° with a slow steam of chlorine

TABLE 1. *The alkoxycarbonylamino-thiols and -sulphonamides, etc.* (I).

				Found (%)				Required (%)			
R	X	M. p.	Formula	C	H	N	S	C	H	N	S
Me	SH	192—194° [a]	$C_4H_5O_2N_3S_2$	25·4	2·6	21·4	—	25·1	2·6	22·0	—
	$SO_2{\cdot}NH_2$	223—224° [a]	$C_3H_6O_4N_4S_2$	20·6	2·3	22·8	26·3	20·2	2·5	23·5	26·9
Et	SH	204—205° [a]	$C_5H_7O_2N_3S_2$	29·0	3·4	19·9	31·5	29·2	3·4	20·5	31·2
	SO_2Cl	148—149° [b]	$C_5H_6O_4N_2ClS_2$	22·4	2·4	15·2	23·4	22·1	2·2	15·5	23·6
	$SO_2{\cdot}NH_2$	226° [a]	$C_5H_8O_4N_4S_2$	24·2	3·2	—	25·1	23·8	3·4	—	25·4
Pr^n	SH	186—187° [c]	$C_6H_9O_2N_3S_2$	33·0	4·5	18·7	—	32·9	4·1	19·2	—
	$SO_2{\cdot}NH_2$	221—222° [a]	$C_6H_{10}O_4N_4S_2$	27·1	4·0	20·8	24·1	27·1	3·8	21·0	24·1
Bu^n	SH	188—190° [c]	$C_7H_{11}O_2N_3S_2$	36·2	4·8	18·3	—	36·0	4·8	18·0	—
	$SO_2{\cdot}NH_2$	197—198° [a]	$C_7H_{12}O_4N_4S_2$	29·8	4·1	20·2	22·8	30·0	4·3	20·0	22·8
n-C_5H_{11}	SH	189—190° [c]	$C_8H_{13}O_2N_3S_2$	39·0	5·2	16·7	26·0	38·9	5·3	17·0	25·9
	$SO_2{\cdot}NH_2$	193° [a]	$C_8H_{14}O_4N_4S_2$	32·8	5·1	18·9	21·4	32·6	4·8	19·0	21·8
n-C_6H_{13}	SH	171—173° [c]	$C_9H_{15}O_2N_3S_2$	41·4	5·4	16·1	24·3	41·4	5·8	16·1	24·5
	SO_2Cl	128—130° [b]	$C_9H_{14}O_4N_2ClS_2$	32·8	4·3	—	Cl 10·2	33·0	4·3	—	Cl 10·8
	$SO_2{\cdot}NH_2$	187—189° [a]	$C_9H_{16}O_4N_4S_2$	35·0	5·0	18·1	20·7	35·1	5·2	18·2	20·8
CH_2Ph	$S{\cdot}CH_2Ph$	179—180° [c]	$C_{12}H_{11}O_2N_3S_2$	54·3	4·2	11·1	16·5	53·9	3·8	10·5	16·0
	$SO_2{\cdot}NH_2$ [d]	217—218° [c]	$C_{10}H_{10}O_4N_4S_2$	38·0	3·3	17·9	20·4	38·2	3·2	17·8	20·4

[a] From H_2O. [b] From $(CH_2Cl)_2$–light petroleum (b. p. 60—80°). [c] From aq. EtOH. [d] Vaughan, Eichler, and Anderson, *J. Org. Chem.*, 1956, **21**, 720.

TABLE 2. *Chlorinations of 2-alkoxycarbonylamino-5-mercapto-1 : 3 : 4-thiadiazoles.*

Reagent	Solvent	Temp.	Time (hr.)	Yields (%) Sulphonyl chloride	Disulphide
Et ester					
Cl_2	70% AcOH	0— 5°	1·75	72	—
,, ...	70% Dioxan	10—15	1·5	50	—
,, ...	70% Bu^{t}OH	10—15	1·75	66	—
n-*Hexyl ester*					
Cl_2	70% AcOH	10—15	1·75	70	—
,, ...	70% ,,	—3— 0	1·75	60	30
,, ...	50% ,,	—2— 0	1·5	—	75
,, ...	70% Bu^{t}OH	10—15	1·75	69—77	—
,, ...	,, ,, (alkaline)	15	1·5	0	98
,, ...	70% Dioxan	10	1·0	60	—
,, ...	50% ,,	10	1·0	Mainly unchanged	
,, ...	100% ,, [a]	10	1·25	0	0
Bu^{t}OCl	90% ,,	10—15	2·5	79	—
,, ...	70% ,,	15	3·5	53	—
NaOCl	75% AcOH	5	3·0	52	44
$PhICl_2$	70% Dioxan	10—15	3·5	70 [b]	—

[a] See text. [b] Estimated yield, converted directly into sulphonamide.

for 1·75 hr. The solids (47·5 g.) were collected, washed with ice-cold water, and air dried. The *sulphonyl chlorides* crystallised from ethylene dichloride–light petroleum (b. p. 60—80°). For this and variants see Table 2.

Di-(2-n-hexyloxycarbonylamino-1 : 3 : 4-thiadiazol-5-yl) Disulphide (III; R = C_6H_{13}).—(*a*) Treatment of 2-*n*-hexyloxycarbonylamino-5-mercapto-1 : 3 : 4-thiadiazole (130 g.) in 50% acetic acid (500 ml.) with chlorine for 1½ hr. at −2° to 0° yielded the *disulphide* (98 g.), m. p.

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187—192° (Found: C, 41·8; H, 5·5; N, 16·2; S, 24·3. $C_{18}H_{28}O_4N_6S_4$ requires C, 41·5; H, 5·4; N, 16·2; S, 24·6%), after crystallisation from ethylene dichloride or aqueous ethanol.

(*b*) The thiol (50 g.) in 40% *tert.*-butyl alcohol (600 ml.) containing sodium hydroxide (7 g.) was treated with chlorine for 1½ hr. at 15°, giving the disulphide (49 g.).

The disulphide (15 g.) in 70% acetic acid (500 ml.) was treated with stirring at 15° with chlorine for 2 hr., giving the sulphonyl chloride (10 g.).

Di-(2-*methoxycarbonylamino*-1 : 3 : 4-*thiadiazol*-5-*yl*) *disulphide* (III; R = Me) had m. p. 246—248° (Found: C, 25·3; H, 2·3; N, 22·2; S, 33·4. $C_8H_8O_4N_6S_4$ requires C, 25·3; H, 2·1; N, 22·1; S, 33·7%), after crystallisation from aqueous ethanol.

Preparation of the Sulphonamides (I; R′ = $SO_2{\cdot}NH_2$).—The crude water-washed sulphonyl chlorides were added to aqueous ammonia (*d* 0·880) or to liquid ammonia, and the sulphonamides purified from water (see Table 1).

2-*Chloro*-5-n-*hexyloxycarbonylamino*-1 : 3 : 4-*thiadiazole* (I; R = C_6H_{13}, R′ = Cl).—(*a*) 5-*n*-Hexyloxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonyl chloride (5 g.) in carbon tetrachloride (30 ml.) was heated with copper bronze (0·1 g.) under reflux for 2 hr. The mixture was taken to dryness, and the solids were extracted with boiling ethanol. Dilution of the extract with water yielded the *chloro-derivative* (2 g.), needles, m. p. 144°, $\lambda_{max.}$ 255 mμ (ε 8909) (Found: C, 40·9; H, 5·1; N, 15·9; Cl, 13·3. $C_9H_{14}O_2N_3ClS$ requires C, 41·0; H, 5·4; N, 15·9; Cl, 13·5%), after purification from aqueous ethanol.

(*b*) The foregoing sulphonyl chloride (1·0 g.) was melted carefully in a free flame and kept molten by intermittent heating for 5 min.; evolution of sulphur dioxide occurred. The residue was crystallised from ethanol to yield the chloro-derivative (0·68 g.).

(*c*) 2-*n*-Hexyloxycarbonylamino-5-mercapto-1 : 3 : 4-thiadiazole (15 g.) in anhydrous dioxan (250 ml.) was treated with chlorine for 75 min. at 10°. The product (7·2 g.), isolated by pouring the mixture into iced water (500 ml.), was purified from ethanol, to yield the chloro-derivative.

2-*Chloro*-5-*ethoxycarbonylamino*-1 : 3 : 4-*thiadiazole*, m. p. 184—185° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 28·9; H, 2·9; N, 20·0; Cl, 17·4. $C_5H_6O_2N_3ClS$ requires C, 28·9; H, 2·9; N, 20·0; Cl, 17·1%), was prepared in 74% yield, by fusion of 5-ethoxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonyl chloride in a free flame for about 2 min., whereafter evolution of sulphur dioxide had ceased.

2-*Acetamido*-5-*chloro*-1 : 3 : 4-*thiadiazole* separated from ethyl acetate in needles, m. p. 245—246° (Found: C, 27·3; H, 2·3; N, 24·0. $C_4H_4ON_3ClS$ requires C, 27·0; H, 2·3; N, 23·7%).

2-n-*Hexyloxycarbonylamino*-1 : 3 : 4-*thiadiazole* (I; R = C_6H_{13}, R′ = H).—5-*n*-Hexyloxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonyl chloride (16·4 g.) was added portionwise with stirring at 20° to 50% hydrazine hydrate solution (60 g., 12 mol.). After 12 hr. at room temperature excess of hydrazine was removed under reduced pressure. Acidification with dilute hydrochloric acid furnished the *product* (10·1 g.), m. p. 95—96° (from ethanol) (Found: C, 47·4; H, 6·2; N, 18·8; S, 14·0. $C_9H_{15}O_2N_3S$ requires C, 47·2; H, 6·6; N, 18·3; S, 14·0%), not depressed on admixture with a sample prepared by reaction of *n*-hexyl chloroformate with 2-amino-1 : 3 : 4-thiadiazole in pyridine.

Action of Hydrochloric Acid and Acetic Anhydride on the Sulphonamides.—(*a*) 5-Acetamido-1 : 3 : 4-thiadiazole-2-sulphonamide (8·5 g.) in concentrated hydrochloric acid (70 ml.) was boiled under reflux for 3½ hr. and the solution taken to dryness under reduced pressure. Crystallisation of the residue from ethanol–ether gave 5-amino-1 : 3 : 4-thiadiazole-2-sulphonamide hydrochloride (5 g.), m. p. 199—200° (decomp.), whose m. p. was not depressed on admixture with authentic material.

(*b*) The acetamido-sulphonamide (2·5 g.) was boiled with acetic anhydride (50 ml.) for 8½ hr. After removal of acetic anhydride under reduced pressure the solids were crystallised from a large volume of ethanol, to yield 2-*acetamido*-5-*hydroxy*-1 : 3 : 4-*thiadiazole* (1·0 g.), m. p. 304° (decomp.) (Found: C, 30·5; H, 3·2; N, 26·6; S, 19·8. $C_4H_5O_2N_3S$ requires C, 30·2; H, 3·2; N, 26·4; S, 20·1%). The last compound was also obtained by the action of acetic anhydride on 1-phenyl-5-thiobiurea and on 1-ethoxycarbonyl thiosemicarbazide as below.

(*c*) A suspension of 1-phenyl-5-thiobiurea (10 g.) in acetic anhydride (40 ml.) containing anhydrous sodium acetate (2 g.) was heated with stirring over a free flame until the vigorous exothermic reaction commenced. The solvent was removed under reduced pressure and the residue extracted with 50% ethanol, to yield 2-acetamido-5-hydroxy-1 : 3 : 4-thiadiazole (1·3 g.). The alcohol-soluble fraction yielded *s*-diphenylurea (1·5 g.) and acetanilide (1·5 g.).

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(*d*) 1-Ethoxycarbonylthiosemicarbazide (22·5 g.) and anhydrous sodium acetate (5 g.) in acetic anhydride (75 ml.) similarly yielded 2-acetamido-5-hydroxy-1 : 3 : 4-thiadiazole (3·65 g.), m. p. 305° (decomp.).

(*e*) 2-Acetamido-5-hydroxy-1 : 3 : 4-thiadiazole (1·8 g.) was heated under reflux with aqueous-ethanolic 4N-hydrochloric acid (45 ml.) until the solids had dissolved and then for a further 30 min., yielding prismatic needles (1·0 g.) of 2-amino-5-hydroxy-1 : 3 : 4-thiadiazole, m. p. 177° (decomp.), $\lambda_{max.}$ 253 mμ (ε 4893) (Found: C, 21·0; H, 2·8; N, 35·5; S, 26·8. Calc. for $C_2H_3ON_3S$: C, 20·5; H, 2·6; N, 35·9; S, 27·3%). The *benzylidene derivative* (from aqueous ethanol) had m. p. 182° (decomp.) (Found: C, 52·6; H, 3·5; N, 20·4. $C_9H_7ON_3S$ requires C, 52·6; H, 3·4; N, 20·5%).

(*f*) 5-Ethoxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonamide (5 g.) was converted into 2-*ethoxycarbonylamino-5-hydroxy*-1 : 3 : 4-*thiadiazole* (1·6 g.), m. p. 263—265° (from aqueous ethanol), $\lambda_{max.}$ 255 mμ (ε 7562) (Found: C, 32·1; H, 3·7; N, 22·0; S, 16·4. $C_5H_7O_3N_3S$ requires C, 31·7; H, 3·7; N, 22·2; S, 16·9%), by hot concentrated hydrochloric acid.

(*g*) 5-*n*-Hexyloxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonamide (4 g.) was recovered unchanged after being heated with N-ethanolic hydrochloric acid (40 ml.) for 2½ hr. When it (10 g.) was heated with ethanolic 3N-hydrochloric acid (200 ml.) for 10 hr., 2-n-*hexyloxycarbonylamino-5-hydroxy*-1 : 3 : 4-*thiadiazole* (3·4 g.), m. p. 242° (decomp.), $\lambda_{max.}$ 255 mμ (ε 7832) (Found: C, 44·6; H, 6·4; N, 16·7; S, 12·9. $C_9H_{15}O_3N_3S$ requires C, 44·1; H, 6·2; N, 17·1; S, 13·1%), was obtained (after crystallisation from aqueous ethanol).

(*h*) When the last-mentioned sulphonamide (5 g.) was boiled under reflux with acetic anhydride (40 ml.) for 7½ hr., sulphur dioxide was evolved and 2-*n*-hexyloxycarbonylamino-5-hydroxy-1 : 3 : 4-thiadiazole (1·4 g.), m. p. 240° (decomp.), was obtained. The same compound (2·4 g.) was formed when 5-*n*-hexyloxycarbonylamino-1 : 3 : 4-thiadiazole-2-sulphonyl chloride (6·55 g.) was heated under reflux with acetic anhydride (40 ml.) for 5 hr.

2-*n*-Hexyloxycarbonylamino-5-hydroxy-1 : 3 : 4-thiadiazole was unchanged by boiling ethanolic 3·5N-hydrochloric acid for 20 hr.

Reactions of 2-*Thiodiurea.*—(*a*) 2-Thiodiurea (10 g.), m. p. 218° (decomp.), $\lambda_{max.}$ 240 mμ (ε 13,530 in H_2O), was gently heated under reflux with concentrated hydrochloric acid (100 ml.) for 15 min., then the acid was removed under reduced pressure. Water (20 ml.) was added, and the solids were collected and washed with cold water (20 ml.). The *product* (5·4 g.), a polymorphic form of the starting material, crystallised from water in prisms, m. p. 204° (decomp.), $\lambda_{max.}$ 240 mμ (ε 13,150 in H_2O) (Found: C, 18·2; H, 4·7; N, 41·6. $C_2H_4ON_4S$ requires C, 17·9; H, 4·5; N, 41·8%). When this product (6 g.) had been heated with concentrated hydrochloric acid (30 ml.) on the steam-bath for 40 min., thiosemicarbazide hydrochloride (3·5 g.), m. p. 186° (decomp.), separated on cooling.

(*b*) 2-Thiodiurea (58 g.) in suspension in acetic acid (100 ml.) and acetic anhydride (200 ml.) was heated under reflux for 1 hr. 2-Acetamido-5-methyl-1 : 3 : 4-thiadiazole (47 g.), m. p. 295—297° (Found: C, 38·2; H, 4·2; N, 27·0. Calc. for $C_5H_7ON_3S$: C, 38·2; H, 4·5; N, 26·7%), was obtained after crystallisation from acetic acid. The foregoing compound (55 g.) was heated on the steam-bath with concentrated hydrochloric acid (100 ml.) for 5 hr., then the acid was removed under reduced pressure. The solids, crystallised from ethanol–ethyl acetate, furnished 2-amino-5-methyl-1 : 3 : 4-thiadiazole hydrochloride hemihydrate, needles, m. p. 108—110° (Found: C, 22·0, 22·3; H, 4·4, 4·8. Calc. for $C_3H_6N_3ClS,\frac{1}{2}H_2O$: C, 22·4; H, 4·4%). The base separated from ethanol in prisms, m. p. 235° (decomp.) (Found: C, 31·2; H, 4·5; N, 36·0. Calc. for $C_3H_5N_3S$: C, 31·3; H, 4·4; N, 36·5%). Reacetylation of the base yielded the original acetyl derivative.

2-n-*Hexyloxycarbonylamino-5-methyl*-1 : 3 : 4-*thiadiazole* separated from aqueous ethanol in flat needles, m. p. 144—145° (Found: C, 49·8; H, 7·4; N, 17·1. $C_{10}H_{17}O_2N_3S$ requires C, 49·4; H, 7·1; N, 17·3%).

5-*Methyl*-1 : 3 : 4-*thiadiazol-2-ylurea* had m. p. 297—298° (decomp.) (Found: C, 30·1; H, 3·7; N, 35·0. $C_4H_6ON_4S$ requires C, 30·4; H, 3·8; N, 35·4%), after crystallisation from ethylene glycol.

2-Thiodiurea (20 g.) was heated under reflux for 1 hr. with propionic acid (75 ml.) and propionic anhydride (50 ml.). After removal of the solvents under reduced pressure, the solids yielded 2-*ethyl-5-propionamido*-1 : 3 : 4-*thiadiazole*, needles, m. p. 225—226° (from ethyl acetate) (Found: C, 46·0; H, 6·1; N, 23·4; S, 17·9. $C_7H_{11}ON_3S$ requires C, 45·4; H, 6·0; N, 22·7; S, 17·3%).

2-Thiodiurea (13·4 g.), heated with 98—100% formic acid (75 ml.) for 20 hr. on the steam-bath, yielded 2-formamido-1 : 3 : 4-thiadiazole, m. p. 221° (decomp.) (from water), identical with authentic material.

The authors thank the Directors of The British Drug Houses Ltd. for permission to publish this work.

CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES LTD., LONDON, N.1. [*Received, November 19th*, 1957.]

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303. *The Hydroxylation of Some αβ-Unsaturated Ketones by Molecular Oxygen.*

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(+)-*epi*-α-Cyperone (Ia) and its 11 : 12-dihydro-derivative (Ib) are autoxidised in the presence of base, to give the 6-hydroxy-ketones in good yield. Under similar conditions (+)-α-cyperone (IX) is dehydrogenated and oxidised to give in small yield a hydroxy-derivative of the trienone (IIIa). Observations are made on the mechanism of oxidation and the influence of the 7-side-chain orientation. (+)-*epi*-α-Cyperone is similarly hydroxylated by the action of alkaline persulphate.

CARDWELL and MCQUILLIN,[1] in examining the action of aqueous-alcoholic alkali on (+)-*epi*-α-cyperone (Ia), obtained a crystalline hydroxylation product, $C_{15}H_{22}O_2$, $\lambda_{max.}$ 250 mμ, ν 3500 (OH), 1653 (>C:C·C:O) and 887 cm.$^{-1}$ (>C:CH_2). Formation of a derivative of the trienone (IIIa) by the action of 2 : 4-dinitrophenylhydrazine in ethanolic hydrochloric acid was taken to indicate hydroxylation at position 6 or 7. Resistance of the hydroxy-ketone to oxidation by manganese dioxide [2] and to isomerisation by alkali to the 3 : 6-diketone as with 6-hydroxy-steroidal 4-en-3-ones [2,3] was thought to contraindicate 6-hydroxylation. Oxidation by chromic acid has now been shown to lead to a diketone which has $\lambda_{max.}$ 257·5 mμ characteristic of the 4-ene-3 : 6-dione (IVa) (cf., *e.g.*, Fieser [4]) and is readily isomerised by alkali to a new diketone, $\lambda_{max.}$ 275·5 mμ, in which the terminal methylene absorption (895 cm.$^{-1}$) of the parent diketone has disappeared. The isomerised diketone is clearly formed from a diketone (IVa) by enolisation and conjugation of the side-chain double bond. The new carbonyl group and the hydroxyl group in the parent hydroxy-ketone must therefore be at position 6. The isomerised diketone would be expected to have a structure (V). Treatment of the parent diketone (IVa) with acid also gave this isomerised product since the ketones (IVa) and (V) gave the same mono-2 : 4-dinitrophenylhydrazone. The orientation of the hydroxyl group in the hydroxy-ketone (IIa) is discussed below.

(+)-11 : 12-Dihydro-*epi*-α-cyperone [5] (Ib) has similarly been found to be autoxidised in aqueous-alcoholic alkali. The product is shown to be the hydroxy-ketone (IIb) by dehydration with 2 : 4-dinitrophenylhydrazine in ethanolic hydrochloric acid to the (+)-β-cyperone derivative [6] (IIIb) and by oxidation to a diketone (IVb). The latter was isomerised with alkali to the more stable 7β-*iso*propyl epimer (VII), and the two diketones (IVb) and (VII) gave the same 2 : 4-dinitrophenylhydrazone.

The hydroxy-ketones (IIa) and (IIb) are formed in the presence of alkali hydroxide, or (see below) in the presence of sodium *iso*propoxide or other bases, and they were recovered

[1] Cardwell and McQuillin, *J.*, 1955, 525.
[2] Cf. Amendolla, Rosenkranz, and Sondheimer, *J.*, 1954, 1226.
[3] Rosenkranz, Velasco, and Sondheimer, *J. Amer. Chem. Soc.*, 1954, **76**, 5024; Ehrenstein, *J. Org. Chem.*, 1940, **5**, 318.
[4] Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4377.
[5] Howe and McQuillin, *J.*, 1956, 2670.
[6] *Idem*, *J.*, 1955, 2423.

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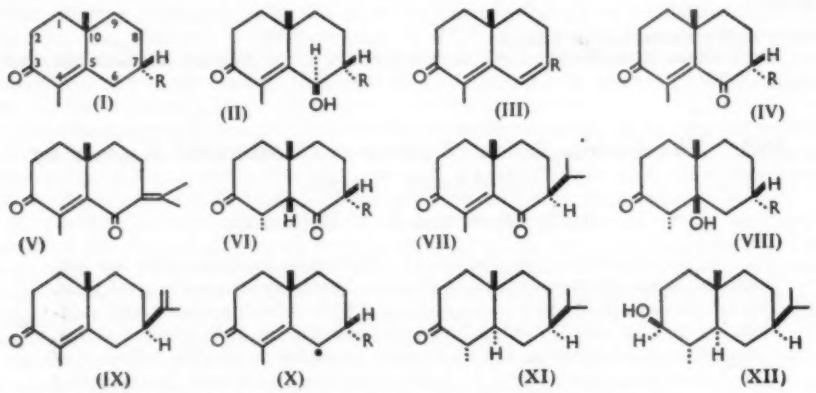
unchanged from refluxing aqueous-alcoholic potassium hydroxide. This resistance to epimerisation at position 6, or to isomerisation to the 3 : 6-dione, which may take up a structure (VI) in which the 7α-substituent is equatorial, is taken to indicate a stable orientation for the 6-hydroxyl group.



(I)—(IV), (VIII), and (X); a, R = $CMe{:}CH_2$; b, R = Pr^i.

(+)-*epi*-α-Cyperone gives [7] an optical rotatory dispersion curve of the same type as, *e.g.*, 8α-testosterone, *i.e.*, ring B is deformed by the large 7α-substituent from a chair towards a boat conformation. Inspection shows that in the boat form, and particularly in intermediate structures, a 6β- introduces less steric interaction than a 6α-substituent. This inversion of the usual order of stability has been encountered by Crawshaw, Henbest, Jones, and Wagland [8] with 11-hydroxy-9β-steroids which also contain a boat *cyclo*hexane ring.

In steroidal 4 : 5-unsaturated 3-ketones a 6β- makes a much more negative rotational contribution than a 6α-hydroxyl substituent.[4,9] This corresponds with Klyne and Stokes's generalisation [12] which Crawshaw, Henbest, Jones, and Wagland were able to apply to their 9β-steroid. The observed differences, ΔM_{5461} for (Ia)–(IIa) and (Ib)–(IIb) are −285° and −345° respectively. A 6β-hydroxyl substituent has also been found [2] to lower the ultraviolet absorption maximum of the 4-en-3-one system by *ca.* 4 mμ and the molar extinction by *ca.* 2000, an effect clearly due to 6β-OH : 10β-Me interaction. For our ketones the results are:

	$\lambda_{max.}$	ε		$\lambda_{max.}$	ε
(Ia)	252·5 mμ	14,450	(Ib)	250 mμ	15,850
(IIa)	250	11,480	(IIb)	247	13,180

Thus, without constituting proof, these three independent lines of argument combine in favouring a 6β-orientation for the hydroxyl group in the ketones (IIa) and (IIb).

Oxygen uptake by the ketones (Ia) and (Ib) effectively ceased after absorption of 1 mol., to give almost exactly 50% of the hydroxy-ketone, together with more highly oxidised, partly acidic material. Addition of sodium dithionite before oxygenation gave a cleaner reaction in which unoxidised material could largely be recovered. Addition of dithionite was designed to remove peroxide which the unsaturated ketones develop in air. An old specimen of (+)-*epi*-α-cyperone (Ia) gave oxidised material from which the 2 : 4-dinitrophenylhydrazone of the trienone (IIIa) could be obtained in small yield, although no crystalline hydroxy-ketone could be isolated.

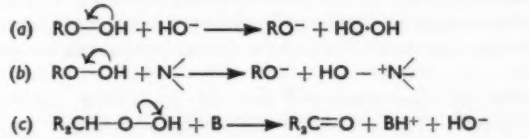
[7] Djerassi, Riniker, and Riniker, *J. Amer. Chem. Soc.*, **1956**, **78**, 6362, 6377.
[8] Crawshaw, Henbest, Jones, and Wagland, *J.*, 1955, 3420.
[9] Balant and Ehrenstein, *J. Org. Chem.*, 1952, **17**, 1587.

As a convenient preparative method, the ketols (VIIIa)[10] and (VIIIb)[5] may be dehydrated and oxidised directly to the respective hydroxy-ketones (IIa) and (IIb) by some hours' refluxing in benzene–propanol–sodium *iso*propoxide in contact with air or oxygen.

These ready oxidations appear to require the enone structure. A related saturated ketone, (+)-tetrahydro-α-cyperone[5] (XI), failed to absorb oxygen when shaken in aqueous-alcoholic alkali and was recovered. Refluxing it in benzene–propan-2-ol with sodium *iso*propoxide similarly failed to effect oxidation, but led, not surprisingly, to a mixture of epimeric alcohols by alkoxide reduction of the keto-group. One of these alcohols was obtained crystalline by way of the 3 : 5-dinitrobenzoate which was conveniently hydrolysed by passage through alkaline alumina.[11] From its manner of preparation and from the rotational change on dinitrobenzoylation[12,13] (ΔM_{5461} + 242°) this tetrahydro-α-cyperol is given the structure (XII) with the 3β-alcohol configuration.

The following observations have been made about the mechanism of these oxidations: (+)-*epi*-α-Cyperone is oxidised to the hydroxy-ketone (IIa) in aqueous piperidine or in dilute aqueous *tert.*-butyl-alcoholic potassium hydroxide, but more slowly than in concentrated aqueous-ethanolic potassium hydroxide. With sodium *tert.*-butoxide in *tert.*-butyl alcohol oxygen uptake is very rapid giving, however, largely acidic and strongly peroxidic products. No measurable oxygen uptake occurred with freshly reduced platinum in ethyl acetate or ethanolic hydrochloric acid [the dihydro-ketone (Ib) was used in the last experiment].

These observations, as well as the position of hydroxylation, point to the enolate ion, but not the conjugate acid, as the oxygen acceptor, either directly or, as in other instances of oxidation of an enol,[14] *via* a mesomeric radical (X). The absence of oxygen uptake in ethyl acetate with platinum, conditions which facilitate oxidation of tetrahydrocarbazoles by a reputedly free-radical mechanism,[15] and the clean reaction after removal of peroxide



with dithionite may be taken to contraindicate, without excluding, a radical mechanism. It is clear, however, that the first product is probably the 6-hydroperoxide (or its anion) which is reduced by hydrolysis[16] (*a*) or, if present, by nitrogenous base:[17] a possible first step is shown at (*b*), or in the presence of strong base attack may be at the methine group[18] as in (*c*).

It is suggested that the extensive oxidation to acidic products in the presence of sodium *tert.*-butoxide is due to reaction (*c*), the rapid oxidation arising from the high enolate concentration.

That oxidation occurs in aqueous *tert.*-butyl alcohol is taken to indicate that autoxidation is not a secondary consequence of attack on the alcohol solvent (as alkoxide ion).

[10] McQuillin, *J.*, 1955, 528.
[11] Castells and Fletcher, *J.*, 1956, 3245.
[12] Klyne and Stokes, *J.*, 1954, 1979.
[13] Barton and Nickon, *J.*, 1954, 4665.
[14] Cf. Robertson and Waters, *J.*, 1948, 1574; Hinshelwood and Shorter, *J.*, 1950, 3276; Shorter, *J.*, 1950, 3425; Speakman and Waters, *J.*, 1955, 40; Allen and Waters, *J.*, 1956, 1132.
[15] Witkop and Patrick, *J. Amer. Chem. Soc.*, 1950, **72**, 633; 1951, **73**, 2188; Witkop, *ibid.*, 1950, **72**, 1428.
[16] Cf. Farmer and Sundralingam, *J.*, 1942, 121.
[17] Riley, Rust, and Vaughan, *J. Amer. Chem. Soc.*, 1948, **70**, 1336; Capp and Hawkins, *J.*, 1953, 4106.
[18] Kornblum and de la Mare, *J. Amer. Chem. Soc.*, 1951, **73**, 880; Agnello, Pinson, and Laubach, *ibid.*, 1956, **78**, 4756.

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This does not exclude oxidation of the alcohol solvent as a possible further mode of reduction of the hydroperoxide.[19]

(+)-α-Cyperone (IX) and (+)-β-cyperone (IIIb) also absorbed oxygen in aqueous-alcoholic alkali, the latter rather slowly, but despite absorption of up to 3 mols. these ketones were largely recovered unchanged. The oxidised material from α-cyperone furnished a crystalline substance A, $C_{15}H_{20}O_2$, $\lambda_{max.}$ 304·5 mμ, $[\alpha]_{5461}$ +764°, in small yield. From the physical constants this is regarded as a hydroxy-derivative of the trienone (IIIa); the position of the hydroxyl group, possibly 2, has not, however, been established. From the oxidation of β-cyperone two crystalline substances, B, $C_{15}H_{20}O_2$, $\lambda_{max.}$ 308·5 mμ, $[\alpha]_{5461}$ +655·4°, and C, $C_{15}H_{22}O_2$, $\lambda_{max.}$ 294·5 mμ, $[\alpha]_{5461}$ +863°, were isolated. The former showed no hydroxyl group absorption in the infrared spectrum and is regarded as a keto-derivative of the parent β-cyperone; substance C may be the corresponding hydroxy-ketone.

Taken together, these experiments indicate that (+)-α-cyperone is converted into the product A by further oxidation of the trienone as intermediate. Formation of the trienone may arise by elimination between a 6β-hydroperoxy-group and the 7α-hydrogen atom or, more probably, by direct transfer of the latter, as hydrion, from the enolate to an acceptor. This is analogous to the known dehydrogenative oxidation of steroidal enones by quinone.[20]

The products A, B, and C account for only a small part of the oxygen consumed. From the amount of unchanged material, in contrast with the oxidation of the *epi*-ketones (Ia) and (Ib), it is clear that the products first formed are in these examples more sensitive to oxidation than the parent ketones. This influence of the stereochemistry at position 7 may be related to the accessibility of the 6α-hydrogen atom in determining the mode of decomposition of a 6-hydroperoxide by route (*c*), followed by further oxidation.

Hydroxylation in good yield has been noted in the alkaline autoxidation of 4 : 4′ : 4″-trinitrotriphenylmethane [19] to the corresponding alcohol. The dehydrogenation of *cyclo*heptadienone by oxygen under strongly alkaline conditions [21] is analogous to the behaviour of (+)-α-cyperone; Ishikawa [22] reports a similar instance in the santonin series, but under acid conditions.

Autoxidation of αβ-unsaturated ketones is known generally to lead to rather complex mixtures.[23] The relatively simple hydroxylation noted above suggested an analogy with the Elbs persulphate oxidation of phenols [24] and of aromatic amines [25] which have reactivity of the same kind as the enol suggested as oxygen acceptor in the present instances. In preliminary experiments this analogy has been verified by oxidation of (+)-*epi*-α-cyperone (Ia) to the same hydroxy-ketone (IIa) by alkaline persulphate and by molecular oxygen. The generality of this reaction is being examined.

Experimental

$[\alpha]_{5461}$ and $\lambda_{max.}$ are for solutions in $CHCl_3$ and EtOH respectively, unless otherwise stated.

Autoxidation of (+)-epi-α-*Cyperone.*—(a) *In air.* Cardwell and McQuillin's procedure [1] was repeated to give, from (+)-*epi*-α-cyperone (1·2 g.), neutral material (0·93 g.), b. p. 120—125°/0·1 mm., n_D^{20} 1·5420, $[\alpha]_{5461}$ +92·4° (*c* 2·6), which by chromatography on alumina gave (+)-6-*hydroxy*-7β(H)*eudesma*-4 : 11-*dien*-3-*one* (IIa) as needles, m. p. 63—64° (0·54 g.) (from light petroleum), $[\alpha]_{5461}$ +88·2° (*c* 4·2) $\lambda_{max.}$ 250 mμ (log ε 4·06) (Found: C, 76·55; H, 9·55. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·4%). This gave (+)-eudesma-4 : 6 : 11-trien-3-one (IIIa)

[19] Cf. Hawthorne and Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 2549.
[20] Wettstein, *Helv. Chim. Acta*, 1940, **23**, 388; Dauben, Eastham, Micheli, Takemura, Mandell, and Chemerda, *J. Amer. Chem. Soc.*, 1953, **75**, 3255; Mandell, *ibid.*, 1956, **78**, 3199; Elks, *J.*, 1954, 468.
[21] Van Tamelen and Hildahl, *J. Amer. Chem. Soc.*, 1956, **78**, 4405.
[22] Ishikawa, *J. Pharm. Soc. Jap.*, 1956, **76**, 507.
[23] Cf. Treibs, *Ber.*, 1930, **63**, 2423 and subsequent papers; Hawkins, *J.*, 1955, 3288.
[24] Cf. Baker and Brown, *J.*, 1948, 2303.
[25] Boyland, Manson, and Sims, *J.*, 1953, 3623; Boyland and Sims, *J.*, 1954, 980.

2 : 4-dinitrophenylhydrazone, m. p. 228° (from ethyl acetate–ethanol), $\lambda_{max.}$ 259, 331, and 417·5 mμ (log ε, 4·15, 4·28, and 4·58) in $CHCl_3$ as previously described.[1]

(b) *Quantitatively in oxygen.* (i) The ketone (0·725 g.) in ethanol (15 c.c.) and water (4 c.c.) with potassium hydroxide (0·8 g.), shaken in oxygen at room temperature, absorbed 101 c.c. (1·2 mol.) in 18 hr. The recovered neutral material (0·6 g.) by chromatography gave pure hydroxy-ketone (0·35 g.), m. p. 63—64°. (ii) The ketone (0·264 g.) in *tert.*-butyl alcohol (15 c.c.) and water (10 c.c.) with potassium hydroxide (0·175 g.) absorbed 26·4 c.c. of oxygen (1 mol.) in 26 hr. to give a neutral product (0·15 g.) from which the hydroxy-ketone was obtained crystalline (m. p. 63°). (iii) The ketone (0·3 g.) in *tert.*-butyl alcohol (20 c.c.) with sodium (0·2 g.) absorbed 1 mol. of oxygen during 0·5 hr. The product, strongly peroxidic to acidified potassium iodide solution, gave an amorphous acidic product (0·2 g.) and only a small amount (0·05 g.) of material, b. p. 130°/0·1 mm., which failed to crystallise. (iv) The ketone in ethyl alcohol (5 c.c.) and water (5 c.c.) with potassium hydroxide (0·4 g.) and sodium dithionite (0·5 g.) rapidly absorbed oxygen (38 c.c.), during oxidation of the dithionite, then a further 23 c.c. during 3 hr. Salts crystallised from the solution which at first became pink and later colourless. Recovery and chromatography gave a hydroxy-ketone fraction (0·15 g.) which crystallised to give material, m. p. 63°. (v) The ketone (0·5 g.) in piperidine (15 c.c.) and water (10 c.c.) absorbed 76 c.c. of oxygen (1·4 mol) during 90 hr. The neutral product (0·43 g.) gave the hydroxy-ketone (0·28 g.) after chromatography. (vi) The ketone (0·86 g.) in ethyl acetate (10 c.c.) added to Adams platinum oxide (0·2 g.) which had been freshly reduced in ethyl acetate (10 c.c.) failed to absorb oxygen when shaken for 24 hr.

(c) *By long storage in air.* The ketone (0·3 g.) which had been stored in a closed tube for 15 months was distilled and chromatographed, to give an oxidised fraction (0·17 g.), b. p. 115—120°/0·1 mm., n_D^{20} 1·5400, $[\alpha]_{5461}$ +168° (*c* 3·0). Redistillation gave a product which afforded a 2 : 4-dinitrophenylhydrazone, m. p. 202°, purified by chromatography to give (+)-eudesma-4 : 6 : 11-trien-3-one 2 : 4-dinitrophenylhydrazone, m. p. 228—229°, identical with that described above.

(+)-7β(H)-*Eudesma*-4 : 11-*diene*-3 : 6-*dione* (IVa).—The hydroxy-ketone from (+)-*epi*-α-cyperone (0·35 g.) in acetic acid (10 c.c.) was treated with chromic acid (0·2 g.) in water (3·5 c.c.) and kept for 12 hr. Recovery gave (+)-7β(H)-*eudesma*-4 : 11-*diene*-3 : 6-*dione* (IVa), b. p. 100—102°/0·1 mm., n_D^{20} 1·5321, $[\alpha]_{5461}$ +399° (*c* 2·42), $\lambda_{max.}$ 257·5 mμ (log ε 4·08), ν 893 cm.$^{-1}$ (Found: C, 77·35; H, 8·8. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%). The *mono*-2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 196—197° (from ethanol), $\lambda_{max.}$ 386·5, 307, and 284 mμ (log ε 4·55, 3·94, 4·18) (Found: C, 61·6; H, 6·0. $C_{21}H_{24}O_5N_4$ requires C, 61·2; H, 5·8%). The diketone (0·1 g.) was recovered unchanged after 1 hour's warming with *o*-phenylenediamine (47 mg.) in ethanol (2 c.c.).

Isomerisation of the Diketone (IVa).—The diketone above (0·25 g.) in ethanol (16 c.c.) and potassium hydroxide (1 g.) in water (2 c.c.) were kept under nitrogen for 15 hr. Recovery gave (+)-*eudesma*-4 : 7(11)-*diene*-3 : 6-*dione*, b. p. 105°/0·1 mm., n_D^{20} 1·5482, $[\alpha]_{5461}$ +59° (*c* 3·0) $\lambda_{max.}$ 275·5 mμ (log ε 4·00) (Found: C, 77·7; H, 8·2. $C_{15}H_{20}O_2$ requires C, 77·6; H, 8·6%), yielding the mono-2 : 4-dinitrophenylhydrazone, m. p. 196—197°, noted above.

Autoxidation of (+)-*Dihydro*-epi-α-*cyperone*.—A solution of (+)-dihydro-*epi*-α-cyperone (1·6 g.) in ethanol (22 c.c.) and water (8 c.c.) with potassium hydroxide (1·6 g.) was kept for 10 days and then gave a neutral product (1·09 g.), b. p. 120—125°/0·1 mm., n_D^{20} 1·5285, $[\alpha]_{5461}$ +50·7° (*c* 4·2). Chromatographed on alumina this gave, by elution with light petroleum–benzene (3 : 1) (+)-6-*hydroxy*-7β(H)-*eudesm*-4-*en*-3-*one* (IIb), needles (0·68 g.), m. p. 90—91° (from pentane), $[\alpha]_{5461}$ +27·2° (*c* 3·5), $\lambda_{max.}$ 247 mμ (log ε 4·12) (Found: C, 76·2; H, 10·5. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). The 2 : 4-dinitrophenylhydrazone was identical with that of (+)-β-cyperone, m. p. 232°. The hydroxy-ketone (55 mg.) in ethanol (5 c.c.) with potassium hydroxide (0·6 g.) in water (1 c.c.) was recovered (42 mg.; m. p. 90—91°) after being refluxed for 5 hr. under nitrogen.

(+)-7β(H)-*Eudesm*-4-*ene*-3 : 6-*dione*.—The above hydroxy-ketone (0·25 g.) in acetic acid (7 c.c.) was kept for 12 hr. with chromic acid (0·14 g.) in water (2·5 c.c.). The product, b. p. 100°/0·1 mm., n_D^{20} 1·5173, crystallised to give as needles, (+)-7β(H)-*eudesm*-4-*ene*-3 : 6-*dione* (IVb), m. p. 80° (from light petroleum), $[\alpha]_{5461}$ +304° (*c* 2·5), $\lambda_{max.}$ 256 mμ (log ε 4·05) (Found: C, 77·3; H, 9·4. $C_{15}H_{22}O_2$ requires C, 77·0; 9·4%). The *mono*-2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 208—209° (from ethanol), $\lambda_{max.}$ 382, 295, 266 mμ (log ε 4·53, 3·94, 4·13) (Found: C, 61·0; H, 6·3. $C_{21}H_{26}O_5N_4$ requires C, 60·9; H, 6·3%).

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Isomerisation of the Diketone (IVb).—The above diketone (0·125 g.) in ethanol (8 c.c.) and water (1 c.c.) with potassium hydroxide (0·5 g.) was kept under nitrogen for 15 hr. Recovery gave (+)-*eudesm-4-ene-3* : 6-*dione* (VII), b. p. 100°/0·1 mm., n_D^{20} 1·5150, $[\alpha]_{5461}$ +169° (*c* 2·7), $\lambda_{max.}$ 254·5 mμ (log ε 4·04) (Found: C, 77·1; H, 9·45. $C_{15}H_{22}O_2$ requires C, 77·0; H, 9·4%). The mono-2 : 4-dinitrophenylhydrazone formed orange needles, m. p. 208—209°, as noted above.

Oxidation of the Ketols (VIIa *and* b) *in Propan-2-ol–Sodium Propoxide.*—(*a*) The *epi*-α-cyperone ketol (VIIIa) (0·7 g.) in benzene (10 c.c.) with sodium *iso*propoxide (from sodium, 0·07 g.) in propan-2-ol (5 c.c.) was heated under gentle reflux during 4 hr. Addition of water and recovery gave material, b. p. 130°/0·1 mm., which crystallised to yield (+)-6-hydroxy-7β(*H*)-eudesma-4 : 11-dien-3-one (IIa), m. p. 63°. (*b*) The dihydro-ketol (VIIIb) similarly afforded the corresponding 6-hydroxy-7β(*H*)-eudesm-4-en-3-one (IIb), m. p. 89° (from pentane).

(+)-4β(H)-*Eudesman*-3β-*ol* (XII).—(−)-4β(H) : 5α(H)-Eudesman-3-one (0·3 g.) in benzene (4 c.c.) was treated with a solution of sodium (0·03 g.) in propan-2-ol (2 c.c.) and refluxed for 8 hr. Recovery gave material, b. p. 95°/0·1 mm., n_D^{20} 1·4943, showing strong absorption at 3380 cm.$^{-1}$ and only weak absorption at 1701 cm.$^{-1}$. Chromatography on alumina gave recovered ketone in small amount (eluant, light petroleum), followed by a product (0·23 g.), b. p. 95°/0·1 mm., n_D^{20} 1·4940, $[\alpha]_{5461}$ −23·3° (*c* 5·7), eluted by benzene–chloroform (4 : 1). This material afforded a 3 : 5-*dinitrobenzoate* as needles, m. p. 173°, $[\alpha]_{5461}$ +58·6° (*c* 3·4), by fractional crystallisation from methanol (Found: C, 62·8; H, 7·1. $C_{22}H_{30}O_6N_2$ requires C, 63·1; H, 7·2%). The dinitrobenzoate, passed through alkaline alumina (cf. Castells and Fletcher [11]) in benzene–light petroleum followed by benzene, gave (+)-4β(H) : 5α(H)-*eudesman*-3β-*ol* (XII), b. p. 95°/0·1 mm., m. p. 73° (from pentane), $[\alpha]_{5461}$ +1·5° (*c* 3·8) (Found: C, 80·4; H, 12·5. $C_{15}H_{28}O$ requires C, 80·4; H, 12·5%).

Autoxidation of (+)-α-*Cyperone.*—(*a*) When (+)-α-cyperone (1·7 g.) in ethanol (40 c.c.) was mixed with potassium hydroxide (2 g.) in water (10 c.c.) and shaken in oxygen, it absorbed 246 c.c. (1·4 mol.) in 26 hr. The neutral material recovered (1·04 g.), b. p. 95—130°/0·1 mm., was chromatographed on alumina, to give (i) by light petroleum–benzene (1 : 1) (+)-α-cyperone (0·86 g.) and (ii), by benzene, material (55 mg.) which afforded yellow prisms, A (16 mg.), m. p. 105°, $[\alpha]_{5461}$ +764° (*c* 2·0), $\lambda_{max.}$ 304·5 mμ (log ε 4·47), from ether–light petroleum (Found: C, 77·9; H, 8·8. Calc. for $C_{15}H_{20}O_2$: C, 77·6; H, 8·6%). (*b*) The ketone (0·77 g.) in ethanol (5 c.c.), water (5 c.c.), and piperidine (10 c.c.) absorbed 250 c.c. of oxygen (3 mol.) during 90 hours' shaking. Recovery and chromatography as above gave recovered α-cyperone (0·49 g.), n_D^{20} 1·5280, $\lambda_{max.}$ 249 mμ (log ε 4·20) and 296—300 mμ (log ε 3·13), and the substance A, m. p. 105°.

Autoxidation of (+)-β-*Cyperone.*—(*a*) The ketone (3·3 g.) in ethanol (45 c.c.), mixed with potassium hydroxide (3·3 g.) in water (14 c.c.), absorbed 498 c.c. of oxygen (1·35 mol.) during 50 hr. Recovery gave 2·15 g. of material, b. p. 100—135°/0·1 mm., which by chromatography gave (i) (+)-β-cyperone (1·56 g.), and (ii), by elution with benzene, an eluate (0·15 g.) which afforded a substance C, pale yellow plates (20 mg.), m. p. 145° (from benzene), $[\alpha]_{5461}$ +863° (*c* 0·9), $\lambda_{max.}$ 294·5 mμ (log ε 4·41) (Found: C, 76·6; H, 9·65. Calc. for $C_{15}H_{22}O_2$: C, 76·9; H, 9·4%). (*b*) (+)-β-Cyperone (1·8 g.) in ethanol (25 c.c.), mixed with potassium hydroxide (1·8 g.) in water (8 c.c.) and kept for 10 days, gave neutral material (1·3 g.), n_D^{20} 1·5627, yielding (i) recovered (+)-β-cyperone (0·7 g.), (ii) substance B (50 mg.), yellow prisms, m. p. 86° (from light petroleum), $[\alpha]_{5461}$ +655·4° (*c* 2·82), $\lambda_{max.}$ 308·5 mμ (log ε 4·36) (Found: C, 77·6; H, 8·8. Calc. for $C_{15}H_{20}O_2$: C, 77·6; H, 8·6%), whose mono-2 : 4-dinitrophenylhydrazone formed red needles, m. p. 233° (from ethyl acetate), $\lambda_{max.}$ 404·5, 328, 258 mμ (log ε 4·63, 3·93, 4·15) (Found: C, 60·7; H, 5·8. Calc. for $C_{21}H_{24}O_5N_4$: C, 61·1; H, 5·8%), and (iii) substance C (4 mg.), m. p. 141°.

Persulphate Oxidation.—A solution of (+)-*epi*-α-cyperone (0·8 g.) in ethanol (20 c.c.) was treated with potassium hydroxide (1 g.) in water (6 c.c.), followed by ammonium persulphate (0·8 g.) in water (5 c.c.). After 48 hr. distillation of the recovered material gave a main fraction, b. p. 120—140°/0·1 mm., n_D^{20} 1·5398, from which (+)-6-hydroxy-7β(H)-eudesma-4 : 11-dien-3-one was obtained (m. p. 64—65°) by chromatography.

One of us (R. H.) is indebted to the Department of Scientific and Industrial Research for an award.

KING'S COLLEGE, NEWCASTLE UPON TYNE. [*Received, August 7th,* 1957.]

304. *The Kinetics and Mechanisms of Aromatic Halogen Substitution. Part VI.* Some Observations relating to Substitution* meta- *to principally* ortho–para-*Directing Substituents; and to Steric Inhibition of Tautomeric Electron Release from the Acetamido-group.*

By P. B. D. de la Mare and M. Hassan.

The rates of chlorination, by molecular chlorine in acetic acid, of 4-acetamidodiphenyl, 1 : 4-diacetamidobenzene, and 2 : 6-dimethylacetanilide are compared with the corresponding rates of chlorination of 2-methylacetanilide, 4-methylacetanilide, *N*-methylacetanilide, *m*-xylene, and benzene. The phenyl and the acetamido-group only slightly deactivate for *meta*-chlorination. The proportion of 6-chloro-derivative formed in the chlorination of 2-methylacetanilide has been determined by isotopic dilution as 20·0%; that of the 4-chloro-derivative in the chlorination of 2 : 6-dimethylacetanilide is 2·6%; and that of 3-chloro-derivative in the chlorination of 4-acetamidodiphenyl is 90%. These values, together with the rate-ratios, allow the effect of steric inhibition of tautomeric electron release from the acetamido-group in these compounds to be estimated.

Interest has recently been renewed [1, 2] in the relationships between the rates of substitution *para* and *meta* to substituents in the benzene ring. For powerfully *ortho–para*-directing substituents, relevant information is difficult to obtain directly, because the proportion of *meta*-substitution is too small, as, *e.g.*, in the nitration of anisole.[3]

One approach [4, 5] involves the study of compounds of the type *p*-R·C_6H_4X, where R is varied, and X is a group more powerfully *ortho–para*-directing than R. Reliable predictive use of the method requires the knowledge that the effects of substituents on the rates of displacements from the benzene nucleus are independent and additive in the free energies of activation for substitution in the various positions. This " additivity hypothesis " has been extensively tested and shown to be a good approximation by Bradfield, Brynmor Jones, and their co-workers [6] for the bromination of phenolic ethers. It seems also to hold reasonably well for the chlorination and bromination of anilides, examined by Orton, Bradfield, Brynmor Jones, and their co-workers,[7–10] provided that the potentially basic nature of anilides [8, 11, 12] is recognised, and, where necessary, allowed for.

Three qualifications relating to the applicability of the additivity hypothesis should be mentioned: (1) It is not to be regarded as numerically accurate for small differences, as Bradfield and Jones [6] observed in comparing the relative reactivities (0·6 : 1) of the compounds (I) and (II). (2) When two substituents are conjugated through the benzene ring (as, *e.g.*, in *p*-nitroacetanilide) their directive influence will be modified by this conjugation, and the additivity principle is likely to break down. As far as we are aware, no

* Part V, de la Mare and Hassan, *J.*, 1957, 3004.

[1] Cf. Brown and Nelson, *J. Amer. Chem. Soc.*, 1953, **75**, 6292; Brown and Smoot, *ibid.*, 1956, **78**, 6255.
[2] de la Mare, *J.*, 1954, 4450.
[3] Bunton, Minkoff, and Reed, *J.*, 1947, 1416.
[4] de la Mare and Vernon, *J.*, 1951, 1764.
[5] Cf. Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons, London, 1953.
[6] Bradfield and Jones, *Trans. Faraday Soc.*, 1941, **37**, 726.
[7] Orton and King, *J.*, 1911, **99**, 1369.
[8] Orton and Bradfield, *J.*, 1927, 986.
[9] Bradfield and Jones, *J.*, 1928, 3080.
[10] Jones, *J.*, 1934, 210.
[11] Dadswell and Kenner, *J.*, 1927, 1106.
[12] Robertson, de la Mare, and Johnston, *J.*, 1943, 276.

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direct kinetic test of this qualification has yet been made, but its influence on product-composition has been discussed (cf. Dewar [13] and de la Mare [14]). (3) The effects of substituents will not be additive when the activation or deactivation of the aromatic nucleus by the substituent involves a tautomeric electron release which is altered by steric interaction with an adjacent substituent. We have now estimated the influence of steric inhibition, by *ortho*-methyl substituents, of tautomeric electron release from the acetamido-group. Further, the effects of a phenyl and of an acetamido-group *meta* to the position of electrophilic substitution have been compared with that of a *meta*-methyl substituent, by comparing the relative rates of chlorination by molecular chlorine in acetic acid of 4-acetamidodiphenyl and of 1 : 4-diacetamidobenzene with those of acetanilide and of 4-methylacetanilide.

Experimental

Acetic acid, m. p. 16·5—16·6°, was prepared by standard methods [7-10, 12] and was stable to chlorine. " AnalaR " benzene was dried (Na) and fractionated, the middle portion, b. p. 80°, being collected. Toluene, b. p. 110°, was purified similarly. The rates of chlorination of these compounds agree well with those recorded elsewhere,[15] the slight difference in temperature and solvent being borne in mind. The following compounds were commercial specimens, or were prepared from commercial specimens of the appropriate amine, distilled when necessary: acetanilide, m. p. 114°; 2-methylacetanilide, m. p. 112°; 4-methylacetanilide, m. p. 153°; 2 : 6-dimethylacetanilide, m. p. 177·5°; 4-acetamidodiphenyl, m. p. 172°; 6-chloro-2-methylacetanilide, m. p. 165°. 1 : 4-Diacetamidobenzene, prepared by Tröger and Westerkamp's method,[16] had m. p. 304°. 4-Chloro-2 : 6-dimethylacetanilide, m. p. 195°, was prepared from the corresponding amine [11] by acetylation with acetic anhydride. 4-Acetamido-3-chlorodiphenyl was prepared by chlorination of 4-acetamidodiphenyl in acetic acid; [17] yield, 62%, m. p. 147° after recrystallisation from aqueous ethanol. Chlorine solutions were prepared by passing dry chlorine into acetic acid. $^{36}Cl_2$ was generated from potassium permanganate and concentrated hydrochloric acid to which $H^{36}Cl$ had been added. The chlorine, after being washed free from hydrogen chloride, was dried (H_2SO_4) and dissolved in acetic acid. Methods of radioactive measurements have already been described.[18] Chlorine in solution was converted into lithium chloride for radioactive counting.

Rate Measurements.—These were carried out by standard methods in blackened bottles. Losses by evaporation were insignificant over the first three samples. The following is an example of a typical run, using 0·01582M-acetanilide and 0·0104M-chlorine: samples (2 ml.) were titrated against 0·00115N-sodium thiosulphate:

Time (min.)	0·0	0·60	1·25	1·78	2·43	3·40	4·49
Titre (ml.)	36·30	23·30	15·60	11·70	8·60	5·90	3·90
k_2 (l. mole^{-1} min.$^{-1}$)	—	54	55	56	57	55	56

The formula $k_2 = 2{\cdot}303\,\{\log_{10} b(a-x)/a(b-x)\}/t(a-b)$ was used to calculate second-order rate coefficients, where a and b are the molarities of aromatic compound and chlorine respectively, and x is the molarity of chlorine consumed at time t.

The rates of reaction of benzene and of toluene, being less rapid and more susceptible to error resulting from volatility, were determined in association with strict blank experiments; [15] the rate ratio, when comparison is made at the same concentration of aromatic compound, is 356, in reasonable accord with those (345, 344) recorded by other workers.[15a, b] Since the second-order rate coefficients are reduced, because the added aromatic compound reduced the ionising power of the solvent,[13] the recorded rate comparisons and partial rate factors have been corrected for this effect; the rate for toluene is included to allow direct comparison to be made with other experimentally available rate sequences.[15]

[13] Dewar, *J.*, 1949, 463.
[14] de la Mare, *J.*, 1949, 2871.
[15] (*a*) de la Mare and Robertson, *J.*, 1943, 279; (*b*) Brown and Stock, *J. Amer. Chem. Soc.*, 1957, **79**, 5175.
[16] Tröger and Westerkamp, *Arch. Pharm.*, 1909, **247**, 663.
[17] Scarborough and Waters, *J.*, 1926, 557.
[18] (*a*) de la Mare and Harvey, *J.*, 1956, **36**, 131; (*b*) de la Mare and Hassan, *J.*, 1957, 3004.

The following is a summary of the observed rate-coefficients, all in acetic acid at 25°.

Compound	ArH (M)	Cl_2 (M)	NaOAc (M)	k_2 (l. mole^{-1} min.$^{-1}$)
Benzene	0·505	0·228	—	$0·75 \times 10^{-4}$
	0·904	0·14	—	$0·61 \times 10^{-4}$
Toluene	0·160	0·093	—	$3·2 \times 10^{-3}$
	0·829	0·142	—	$2·3 \times 10^{-3}$
Acetanilide	0·0158	0·0105	—	56
	0·0113	0·00452	—	56
4-Methylacetanilide	0·0169	0·00451	—	92
	0·0135	0·00450	—	92
2-Methylacetanilide	0·0221	0·00510	—	11·5
	0·0309	0·00956	—	11·7
4-Acetamidodiphenyl	0·0629	0·0393	—	15·2
	0·0553	0·0244	—	14·5
1 : 4-Diacetamidobenzene	0·0167	0·00806	—	13·7
	0·0114	0·00749	—	14·0
2 : 6-Dimethylacetanilide	0·0918	0·0697	0·0100	0·70
	0·0648	0·0688	—	0·71
	0·147	0·0827	—	0·73

Analysis of Products.—By isotopic dilution it has been shown that 2 : 6-dimethylacetanilide (0·0506M) and chlorine (0·04434M) in acetic acid give 2·6% of 4-chloro-2 : 6-dimethylacetanilide calculated on the consumption of chlorine. The main product is 3-chloro-2 : 6-dimethylacetanilide, which was isolated in a separate experiment, m. p. 146—147°, in over 80% yield.

Chlorination of 2-methylacetanilide (0·045M) with chlorine (0·0361M) in acetic acid similarly gives 20·0% of 6-chloro-2-methylacetanilide, and 4-acetamidodiphenyl (0·063M) with chlorine (0·051M) in acetic acid gives 90·0% of 4-acetamido-3-chlorodiphenyl.

Discussion

Kinetics and Mechanism.—Reactions of chlorine with aromatic compounds have uniformly been found [6-10,15] to be of the kinetic form $-d[Cl_2]/dt = k_2[ArH][Cl_2]$, but this is slightly disturbed by the hydrogen chloride produced in the reaction, acting (*a*) as an electrolyte, accelerating the reaction by virtue of an increase in the ionising power of the medium; and (*b*), for basic substrates, as an acid, removing the reactant as the salt. The rate-coefficients used for comparison in this work have been determined, as far as possible, towards the early stages of reaction to minimise these disturbances, which indeed are quite small, as is shown, for example, by the rate of chlorination being only slightly influenced by the presence of a base, sodium acetate.

The effects of electrolytes on the rates of chlorination [15, 19] have been interpreted [15, 19, 20] as demonstrating that the reaction involves molecular chlorine as the electrophilic reagent, rather than chlorine acetate or " positive chlorine," and this conclusion is herein adopted, since the effects both of acids and of bases accord with those earlier established for other systems.

The rate coefficients now recorded for acetanilide and 2- and 4-methylacetanilide agree well with those recorded by Orton and Bradfield,[8] after allowance for the difference in solvent. The relative reactivity of acetanilide and *N*-methylacetanilide is derived from this work and that of Bradfield and Jones; [9] the value for the rate of chlorination of *m*-xylene is obtained by comparison with the data recorded by Robertson *et al.*[19]

Products of Reactions.—The products of monochlorination of acetanilide by chlorine in acetic acid were studied carefully by Orton and Bradfield.[8] There are formed 67·5% of 4- and 32·5% of 2-chloroacetanilide. The acetamido-group is so strongly *ortho–para*-directing that the position of substitution in 4-methylacetanilide must be *ortho* to the acetamido-group.

The only recorded product of monochlorination, in acetic acid, of 2-methylacetanilide is 4-chloro-2-methylacetanilide, isolated in 74% yield.[21] If the principle of additivity of

[19] Robertson, Dixon, Goodwin, McDonald, and Scaife, *J.*, 1949, 294.
[20] Robertson, *J.*, 1954, 1267.
[21] Lellman and Klotz, *Annalen*, 1885, **231**, 317; Claus and Stapelberg, *ibid.*, 1893, **274**, 286.

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substituent effects held, the 6-chloro-derivative would also be obtained, in about half the yield found in the 2-chlorination of acetanilide, and accordingly it would be predicted that 79·6% of 4- and 19·4% of 6-chloro-2-methylacetanilide would be produced in this reaction. The present results indicate that the proportion of the latter is 20·0%, in excellent agreement with the prediction.

The products of chlorination of 2 : 6-dimethylacetanilide do not seem to have been investigated in detail. Nitration gives the 3-nitro-derivative,[22] but this could be because the anilide is converted, under the conditions used for nitration, into the salt, and the two methyl groups would then automatically control the orientation. Bromination apparently gives 4-bromo-2 : 6-dimethylacetanilide, with some of the 3-isomer.[11] The main product of chlorination by molecular chlorine in acetic acid has been found [23] to be the 3-chloro-derivative, which can be isolated in excellent yield nearly pure. Isotopic dilution has now shown that 2·6% of the 4-chloro-isomer is formed in the reaction. Thus, for this reaction, the two methyl groups, rather than the acetamido-group, dominate the orientation.

Chlorination of *m*-xylene under the conditions of the kinetic measurements, gives 77% of the 4-chloro-derivative,[15b; cf. 24] a value in reasonable agreement with that (73%) calculated on the basis of additivity (cf. ref. 25).

Chlorination of *N*-methylacetanilide also has not been investigated in detail. For the purpose of the discussion, we adopt the view, least favourable though it is for the argument developed, that all the substitution in this compound is in the 4-position, since acetanilide gives 67% of 4-chlorination, and the extra *N*-methyl substituent is likely to impede 2-chlorination in the former compound.

The only recorded product of monochlorination of 4-acetamidodiphenyl is the 3-chloro-compound; [17] analysis by isotopic dilution has now shown that 90% of this material is produced in this reaction under conditions similar to those used for the kinetic measurements.

Partial Rate Factors for Chlorination.—The relative rates and product compositions discussed above allow the following tabulation of rates and partial rate-factors for chlorination in acetic acid at 25°.

R at position					10^{-5} × Partial rate factor at position					10^{5} × Rel. rate (PhH = 1)
1	2	3	4	6	2	3	4	5	6	
NHAc	H	H	H	H	6·1	—	25·2	—	6·1	6·2
,,	H	H	Me	H	31	—	—	—	31	10·2
,,	H	H	Ph	H	4·5	—	—	—	4·5	1·65
,,	H	H	NHAc	H	2·3	2·3	—	2·3	2·3	1·5
,,	Me	H	H	H	—	—	6·2	—	1·56	1·29
,,	Me	H	H	Me	—	0·23	0·012	0·23	—	0·079
Me	H	Me	H	H	2·6	—	4·3	—	4·3	1·85
NMe·Ac	H	H	H	H	—	—	0·02	—	—	~0·0033

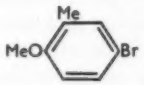
In the following discussion, we adopt the view that the principle of additivity of free energy changes as determined by substituents is a good first approximation, and that any large divergences from predictions based on this principle can be discussed in terms of the qualifications mentioned above.

Activation by the meta-*Methyl Substituent.*—Comparison of the rate of substitution *ortho* to the acetamido-group in 4-methylacetanilide (31×10^5) and acetanilide ($6{\cdot}1 \times 10^5$) shows that a methyl substituent increases the rate of substitution in the *meta*-position by a factor of about 5·1. This accords excellently with Brown and Stock's recent direct determination (5·0), the rate and proportion of *meta*-substitution in the chlorination of toluene being used.[15b]

Steric Inhibition of Tautomeric Electron-release.—On this basis, the partial rate-factors for 4- and 6-chlorination of 2-methylacetanilide should be 125×10^5 and 31×10^5

[22] Noelting, Braun, and Thesmar, *Ber.*, 1901, **34**, 2261.
[23] Beard and Hickinbottom, *Chem. and Ind.*, 1957, 1421.
[24] Kobe and Brennecke, *Ind. Eng. Chem.*, 1954, **46**, 728.
[25] Condon, *J. Amer. Chem. Soc.*, 1948, **70**, 1963.

respectively, whereas the observed figures are $6{\cdot}2 \times 10^5$ and $1{\cdot}6 \times 10^5$ respectively, *i.e.*, a diminution by a factor of 20. This is most reasonably interpreted as the result of steric inhibition of tautomeric electron-release from the acetamido-group, resulting from interference of the 2-methyl substituent with the hydrogen atom of the NH-group (III). Steric inhibition of tautomeric electron-release in *N*-methylacetanilide is likely to be, to a good



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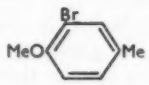

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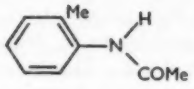

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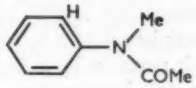

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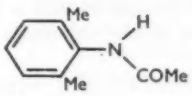

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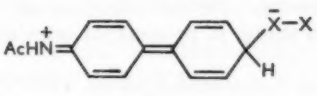

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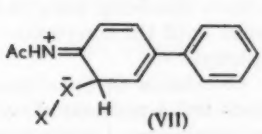

(VII)

approximation, of magnitude similar to that in 2-methylacetanilide, since in each case the extra impedance to the reaction results from interference between similarly placed methyl and hydrogen substituents (III and IV). On this account, therefore, *N*-methylacetanilide should have its reactivity reduced below that of acetanilide by a factor of about 20. In fact, it is less reactive than acetanilide by a factor of 1200; this further change, by a factor of about 60, is in the direction opposite to that expected on the basis of polar effects, but it accords with Robertson, de la Mare, and Swedlund's [26] suggestion that N–H hyperconjugation makes a significant contribution to the reactivity of acetanilide.

The introduction of a second methyl substituent *ortho* to the acetamido-group increases still further the steric hindrance to the tautomeric electron-release from the latter group. Situations of this kind have been discussed by Wepster [27] with reference to other properties, including ultraviolet spectra and reactivities, of this and related compounds. Product-analysis by isotopic dilution shows that, for chlorination, only 2·6% of the product is the 4-chloro-derivative. After allowance for activation of this position by the methyl substituents, the reactivity *para* to the acetamido-group is reduced in this compound, as compared with 2-methylacetanilide, by a factor of $5 \times 6{\cdot}2 \times 10^5/0{\cdot}012 \times 10^5$, *i.e.*, *ca.* 2600. This figure is considerably larger than that (20) representing the effect of the first methyl group, because the interference of the *ortho*-methyl substituent with the COMe group is greater than that with hydrogen (V).

Polar Effect of the meta-*Acetamido-group.*—The present experiments enable two separate estimates to be made of the effect of the *meta*-acetamido-group. First, in 1 : 4-diacetamidobenzene the partial rate factor ($2{\cdot}3 \times 10^5$) compared with that in the *ortho*-position in acetanilide ($6{\cdot}1 \times 10^5$) shows that the substituent decreases the rate of substitution *meta* to it by a factor of 2·7. This is in the direction of overall electron-withdrawal, and shows that, in the *meta*-position, the inductive effect of this substituent is quantitatively more important than " second-order relay " of the tautomeric effect to the *meta*-position. The latter effect is not absent, however, as can be seen by the fact that the rate of substitution [15b] in the 4-position in *m*-xylene ($4{\cdot}3 \times 10^5$) is reduced in the corresponding position in 2 : 6-dimethylacetanilide to $0{\cdot}23 \times 10^5$, *i.e.*, by a factor of 19. This difference (roughly a factor of 7) is to be associated with the reduction, by the *ortho*-methyl substituents, of the tautomeric electron-release from the acetamido-group. This tautomeric electron-release is, however, not in this system reduced to zero; the reactivity

[26] Robertson, de la Mare, and Swedlund, *J.*, 1953, 782.
[27] Wepster, in " Progress in Stereochemistry, II," ed. Klyne and de la Mare, Butterworths, 1958, in the press.

of the 4-position in 2 : 6-dimethylacetanilide is faster than that which would be expected *meta* to two methyl groups by a factor of about $0{\cdot}012 \times 10^5/5 \times 5$, *i.e.*, *ca.* 50; so even for the *meta*-position the acetamido-group in acetanilide must be contributing, by its tautomeric effect, an electron-release corresponding with a factor of considerably more than 7, a still larger electron-withdrawing effect being superimposed upon this.

Polar Effect of a meta-*Phenyl group.*—Comparison of the rate of *ortho*-chlorination in acetanilide ($6{\cdot}1 \times 10^5$) with the appropriate partial rate-factor for chlorination in 4-acetamidodiphenyl ($4{\cdot}5 \times 10^5$) enables us to deduce that the phenyl group is deactivating for this reaction by a factor of 1·3. This is considerably smaller than the corresponding factor for bromination by positive bromine.[18b] This result is consistent with the theory [2,18,28] that the inductive effects of substituents are more important in halogenations involving positively charged reagents, whereas the tautomeric effects are more important in those involving halogen molecules. Further discussion of the present results is postponed until the completion of a study, in progress, of orientation in the chlorination of diphenyl.

Orientation in Substitution in 4-Acetamidodiphenyl.—For chlorination and nitration, the 2- and 4-positions of acetanilide are activated to comparable extents, so that both 2- and 4-substituted derivatives are obtained from these reactions. Similar substitution in 4-acetamidodiphenyl requires discussion of the possibility that the activating power of the 4-substituent will be transmitted to the 4′-position of the unsubstituted ring through structures of the type shown in (VI). Since the alternative structure for 3-substitution avoids compression of the 2 : 2′-hydrogen atoms, and maintains the full aromatic resonance of the second ring, it is not surprising that reactions through transition states like (VII) are favoured—in the present experiments, in proportions which must be at least 4·5 : 1 when the statistical factor is included.

The present results confirm that there is a greater spread in reactivities for bromination in acetic acid than for chlorination; the overall rate-ratio, acetanilide : benzene, is $6{\cdot}2 \times 10^5$ for the latter reaction, but is at least 10^8 for bromination.[12,15]

In Part V,[18b] we discussed the difference in $\frac{1}{2}o$: *p*-ratio between that for nitration of diphenyl in acetic anhydride at 0° (1·7; Dewar *et al.*[29]) and that for bromination by positive bromine in aqueous dioxan (0·68). The theoretical discussion was based in part on this comparison, and remains valid, except specifically in regard to the following proviso.

Professor F. Bell, of the Heriot-Watt College, Edinburgh, has pointed out to us that Jenkins, McCullough, and Booth [30] obtained, for nitration of diphenyl by a mixture of nitric and sulphuric acid at high temperatures, a $\frac{1}{2}o$: *p*-ratio in the neighbourhood of 0·5. We are indebted to Professor Bell for pointing out to us that we had misinterpreted their description. It seems that the nitration of diphenyl may be more dependent on the conditions of reaction than we had realised, but it seems also that it is not yet determined whether this dependence is a function of the reagent, temperature, or other variables.

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[28] de la Mare and Robertson, *J.*, 1948, 100.
[29] Dewar *et al.*, *J.*, 1956, 3572, 3576, 3581.
[30] Jenkins, McCullough, and Booth, *Ind. Eng. Chem.*, 1930, **22**, 31.

305. *The Synthesis of Indolo(2′ : 3′-1 : 2)- and Indolo(3′ : 2′-1 : 2)-carbazole.*

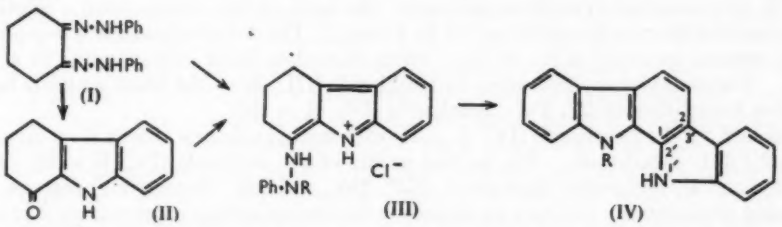
By Frederick G. Mann and Trevor J. Willcox.

It is shown that 1 : 2 : 3 : 4-tetrahydro-1-oxocarbazole, which is feebly basic, forms a very unstable phenylhydrazone but a stable yellow phenylhydrazone hydrochloride, which when heated under reduced pressure or in acetic acid solution, undergoes indolisation and dehydrogenation to give indolo(2′ : 3′-1 : 2)carbazole.

Tetrahydro-4-oxocarbazole is more strongly basic and its pure crystalline hydrochloride can be isolated. It also forms a stable colourless phenylhydrazone hydrochloride, which when similarly heated gives indolo(3′ : 2′-1 : 2)carbazole.

The structures of the two oxocarbazoles, their salts and their phenylhydrazone hydrochlorides are discussed.

It has been shown by Plancher, Cecchetti, and Ghigi [1] that hot dilute sulphuric acid reacts with *cyclo*hexane-1 : 2-dione bisphenylhydrazone (I), causing indolisation of one hydrazone unit and hydrolysis of the other, to form 1 : 2 : 3 : 4-tetrahydro-1-oxocarbazole (II) a detailed study of this production of the oxo-carbazole (II) has been made by Bloink and Pausacker.[2] The indolo(2′ : 3′-1 : 2)carbazole system was first synthesised as the 9-methyl derivative (IV; R = Me) by Brunton, Drayson, Plant, and Tomlinson [3] using a less direct route.



Bhide, Tikotkar, and Tilak,[4] in a recent preliminary note, have shown that the oxocarbazole (II) reacts with phenylhydrazine in boiling acetic acid, undergoing indolisation and dehydrogenation, to furnish the parent indolo(2′ : 3′-1 : 2)carbazole (IV; R = H).

We have also investigated the formation of the ring-system (IV), and find that an ethanolic solution of the bisphenylhydrazone (I), when heated with hydrogen chloride, readily deposits stable yellow crystals of composition corresponding to tetrahydro-oxocarbazole phenylhydrazone hydrochloride. The free phenylhydrazone is markedly unstable and apparently has not been recorded, but a solution of the colourless oxo-carbazole and phenylhydrazine in ethanolic hydrogen chloride when heated also deposits the yellow crystalline hydrochloride. Since, however, it is highly improbable that 1-oxocarbazole phenylhydrazone would form a stable coloured salt by simple proton addition to any of the nitrogen atoms, there is little doubt that the hydrochloride has the structure (III; R = H), and that both the colour and the stability are associated with the conjugated system so produced. The infrared spectrum of the hydrochloride shows the bands at 3140 and 2600 cm.$^{-1}$, indicating the presence of the $=NH$ and the $\equiv NH^+$ group respectively: although this evidence does not preclude the structure (V; R = H), the contribution by this form is probably for the above reasons almost negligible.

[1] Plancher, Cecchetti, and Ghigi, *Gazzetta*, 1929, **59**, 346.
[2] Bloink and Pausacker, *J.*, 1950, 1328.
[3] Brunton, Drayson, Plant, and Tomlinson, *J.*, 1956, 4783.
[4] Bhide, Tikotkar, and Tilak, *Chem. and Ind.*, 1957, 363.

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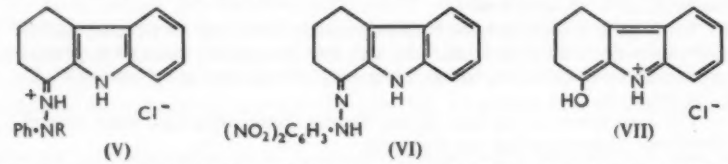
Tetrahydro-1-oxocarbazole (II) reacts similarly with *N*-methyl-*N*-phenylhydrazine in ethanolic hydrogen chloride to give the yellow hydrochloride (III; R = Me), which, like the previous salt, can be recrystallised unchanged from ethanol: its infrared spectrum also shows bands at 3140 and 2600 cm.$^{-1}$.

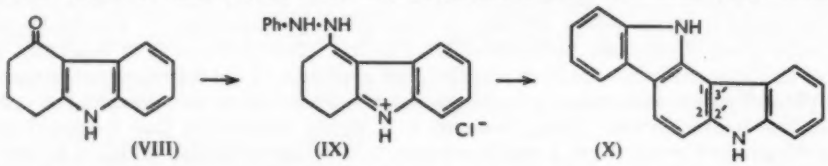
In contrast to these results, the oxocarbazole (II) gives a normal, purple 2 : 4-dinitrophenylhydrazone (VI). When hydrogen chloride is passed into a suspension of this compound in cold acetone, a clear yellow solution is slowly obtained, but dilution with ether then rapidly restores the purple colour. The yellow colour is probably that of an unstable hydrochloride, which dissociates on dilution of the hydrogen chloride solution. It is noteworthy that an ethereal solution of the oxocarbazole (II), when treated with hydrogen chloride, deposits a yellow crystalline hydrochloride (VII), which rapidly dissociates when separated from the solution. Plant, Mears, and Oakeshott [5] have reported that both the oxocarbazole (II) and its colourless 6-bromo-derivative give yellow hydrobromides, too unstable for isolation: these salts undoubtedly have a similar structure.



The phenylhydrazone hydrochloride (III; R = H), when heated at 320°/0·2 mm., undergoes indolisation and dehydrogenation, affording indolo(2′ : 3′-1 : 2)carbazole (IV; R = H) as a colourless crystalline sublimate: the same process occurs when a solution of the hydrochloride in acetic acid is boiled for 5 hours. The dehydrogenation was confirmed by the infrared spectrum of the product, which showed no band corresponding to a $>CH_2$ group. The methylphenylhydrazone hydrochloride (III; R = Me) when similarly heated furnishes 9-methylindolo(2′ : 3′-1 : 2)carbazole (IV; R = Me).

Indolo(2′ : 3′-1 : 2)carbazole (IV; R = H) with methyl sulphate affords 1′ : 9-dimethylindolo(2′ : 3′-1 : 2)carbazole. The melting points of the carbazole (IV; R = H) and its 9-methyl and 1′ : 9-dimethyl derivatives (370°, 245°, and 209°, respectively) decrease with increasing methylation: this may be caused by the methyl groups progressively decreasing the degree of hydrogen-bonding, or even forcing the molecule out of the planar configuration.

1 : 2 : 3 : 4-Tetrahydro-4-oxocarbazole (VIII), when heated with phenylhydrazine in ethanol with the addition initially of a trace of acetic acid and later of ethanolic hydrogen chloride, gives colourless crystals of the phenylhydrazone hydrochloride (IX), which is also sufficiently stable to be recrystallised from ethanol. This salt differs in structure from its yellow isomer (III; R = H) in having a shorter conjugated chain and no *o*-quinonoid ring, and it is these factors which are responsible for its absence of colour.



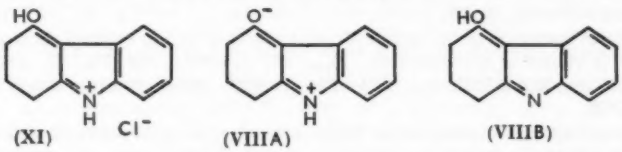
The hydrochloride (IX), when heated at 360°/0·2 mm., similarly undergoes indolisation and dehydrogenation to give indolo(3′ : 2′-1 : 2)carbazole (X); boiling acetic acid, however, does not produce this series of reactions. The properties of our indolo(3′ : 2′-1 : 2)carbazole (X) show that it is almost certainly identical with that which Tomlinson [6] prepared by the

[5] Plant, Mears, and Oakeshott, *J.*, 1934, 273.
[6] Tomlinson, *J.*, 1951, 809.

di-indolisation and subsequent dehydrogenation of bis*cyclo*hexanone *m*-phenylenedihydrazone, and afford additional evidence that her synthesis does furnish this compound and not the possible alternative indolo(2′ : 3′-2 : 3)carbazole.

Bhide *et al.*[4] report that the 4-oxocarbazole (VIII) was unaffected when its solution in acetic acid containing phenylhydrazine was boiled, and they were unable to prepare its phenylhydrazone or to indolise the phenylhydrazone of 1 : 2 : 3 : 4-tetrahydro-9-methyl-4-oxocarbazole.

Tetrahydro-4-oxocarbazole (VIII), when treated in cold ethereal solution with hydrogen chloride, deposits a colourless hydrochloride which can be collected and kept unchanged over calcium chloride at atmospheric pressure for several days. Exposure under reduced pressure causes slow dissociation, and its melting point indicates complete dissociation on heating. There can be little doubt that the hydrochloride has the structure (XI). The 4-oxocarbazole (VIII) is, therefore, more strongly basic than the 1-oxocarbazole (II).



(XI) (VIIIA) (VIIIB)

It should be noted that the infrared spectra of both the 4-oxocarbazole (VIII) and its hydrochloride (XI) present indefinite features. The spectrum of the carbazole has a strong band at 1610 cm.$^{-1}$, and a rather broad band at 3060 cm.$^{-1}$. Alternative interpretations of these bands may be made: (*a*) although the band at 1610 cm.$^{-1}$ has an exceptionally low value for a >CO band, and that at 3060 cm.$^{-1}$ is unusually broad for an >NH band, these properties are consistent with existence of the carbazole as a resonance hybrid (VIII ⟷ VIIIA), particularly if some additional hydrogen-bonding is present; (*b*) the bands at 1610 and 3060 cm.$^{-1}$ might be due to an >N– group and an OH group respectively, indicating the structure (VIIIB). The hydrochloride (XI) has a broad band with peaks at 2930 and 2880 cm.$^{-1}$, which may indicate an OH band partly overlaid by CH or CH_2 bands, and a band at 2230 cm.$^{-1}$ which in spite of its low value might represent the $\geq NH^+$ group.

In contrast, the spectrum of tetrahydro-1-oxocarbazole (II) shows a strong sharp band at 3275 cm.$^{-1}$, due to the >NH group, and a strong band at 1642 cm.$^{-1}$ attributed to the >CO group.

Experimental

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxocarbazole Phenylhydrazone Hydrochloride* (III; R = H).—(*A*) A solution of *cyclo*hexane-1 : 2-dione bisphenylhydrazone (10 g.) in warm ethanol (225 c.c.) was treated with saturated ethanolic hydrogen chloride (20 c.c.), then heated on a steam-bath until separation of the crystalline hydrochloride was complete (10—15 min.). The mixture was cooled to 0°, and the yellow hydrochloride collected and twice recrystallised from much ethanol; it had m. p. 182—183° (decomp.), resolidifying to a reddish-brown solid which did not melt below 360° (Found: C, 69·6; H, 5·9; N, 13·7. $C_{18}H_{17}N_3$,HCl requires C, 69·35; H, 5·8; N, 13·5%). The yields of crude material were variable (50—75%) and in one experiment attained 89%. The salt is insoluble in hot water and almost insoluble in most organic solvents.

(*B*) A solution of 1-oxocarbazole (II) (0·2 g.) and phenylhydrazine (0·12 g., 1·1 mol.) in ethanol (5 c.c.) was mixed with saturated hydrogen chloride (5 c.c.), boiled under reflux for 30 min., and cooled to 0°. The deep yellow crystals of the hydrochloride (III; R = H) (0·1 g.), when collected, washed with water, and once recrystallised from ethanol, had m. p. 180—182° (decomp.), unaffected by admixture with the above product.

The hydrochloride, when treated with aqueous sodium hydroxide, gave the free hydrazone, which rapidly darkened and decomposed.

1 : 2 : 3 : 4-*Tetrahydro*-1-*oxocarbazole* N-*Methyl*-N-*phenylhydrazone Hydrochloride* (III; R = Me).—A solution of 1-oxocarbazole (1 g.) and *N*-methyl-*N*-phenylhydrazine (0·8 g., 1·2 mol.) in warm ethanol (25 c.c.), when treated with saturated ethanolic hydrogen chloride (5 c.c.),

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rapidly deposited yellow crystals of the ***hydrochloride hemihydrate*** (0·74 g., 42%), m. p. 181—182° (decomp.) (from ethanol) (Found, on independent samples: C, 68·0, 68·4; H, 6·1, 6·0. $C_{19}H_{19}N_3$,HCl,0·5H_2O requires C, 68·2; H, 6·3%).

Tetrahydro-1-oxocarbazole 2 : 4-*dinitrophenylhydrazone* (VI) was readily formed in ethanol, and separated as purple crystals, m. p. 299—301° (decomp.), from much dioxan (Found: C, 59·0; H, 4·2. $C_{18}H_{15}O_4N_5$ requires C, 59·2; H, 4·1%).

Indolo(2′ : 3′-1 : 2)carbazole (IV; R = H).—(*A*) The hydrochloride (III; R = H) (1 g.) was heated in an inclined glass tube at 0·2 mm., the temperature being increased slowly to 320°. Sublimation was complete in *ca.* 15 min., leaving only a trace of residual yellow resin. The sublimate was washed with water, dried (yield, 0·75 g., 90%), recrystallised from ethanol, and resublimed, giving the indolocarbazole (IV; R = H) as colourless crystals, m. p. 370° (lit.,[4] 371°) (Found: C, 84·8; H, 4·6; N, 11·2. Calc. for $C_{18}H_{12}N_2$: C, 84·4; H, 4·7; N, 10·9%).

(*B*) A solution of the hydrochloride (0·2 g.) in acetic acid (10 c.c.) was boiled under reflux for 5 hr., the indolocarbazole separating after *ca.* 1 hr. The solution was concentrated and cooled, and the indolocarbazole collected and washed with water (0·1 g., 60%); after sublimation it had m. p. and mixed m. p. 370°.

The ultraviolet spectrum of the indolo(2′ : 3′-1 : 2)carbazole in ethanol showed the following characteristics (ε values in parentheses): $\lambda_{max.}$ 257 (75,600), 269 (75,510), 285 (34,100), 324 (29,750), 340 (9060), 357 (4760), $\lambda_{min.}$ 263—264 (71,600), 280·5 (29,410), 296 (7710), 335—337 (8725), 351 (3760).

The indolocarbazole was unaffected when heated with palladium–charcoal, alone or in *p*-cymene. Its ethanolic solution showed a violet fluorescence and readily gave a dipicrate, m. p. 203—204° (lit.,[4] 202°), red-brown needles (Found: N, 15·45. Calc. for $C_{18}H_{12}N_2$,$2C_6H_3O_7N_3$: N, 15·3%).

9-Methylindolo(2′ : 3′-1 : 2)carbazole (IV; R = Me).—The hydrochloride (III; R = Me), when similarly heated at 350°/0·2 mm., gave a sublimate which, when purified as before, furnished the indolocarbazole, colourless prisms, m. p. 244—245° (lit.,[3] 243—244°) (Found: C, 84·3; H, 5·4; N, 10·5. Calc. for $C_{19}H_{14}N_2$: C, 84·4; H, 5·2; N, 10·4%).

1′ : 9-Dimethylindolo(2′ : 3′-1 : 2)carbazole.—Saturated aqueous sodium hydroxide solution (0·1 c.c.) was added to a mixture of the carbazole (IV; R = H) (0·2 g.), methyl sulphate (0·22 g., 2·2 mols.), and acetone (1 c.c.), which was shaken for 30 min., rapidly giving a clear solution which then deposited crystals. The mixture was poured into water. The precipitated, colourless, almost pure *dimethylindolocarbazole* (0·2 g., 90%) formed needles, m. p. 209°, from aqueous acetone (Found: C, 84·5; H, 5·7; N, 10·15. $C_{20}H_{16}N_2$ requires C, 84·5; H, 5·7; N, 9·85%). An ethanolic solution showed a violet fluorescence in ultraviolet light.

1 : 2 : 3 : 4-Tetrahydro-4-oxocarbazole Phenylhydrazone Hydrochloride (IX).—A mixture of 4-oxocarbazole (VIII) (1·5 g.), phenylhydrazine (0·88 g., 1·1 mols.), acetic acid (0·1 c.c.), and ethanol (80 c.c.) was boiled under reflux for 24 hr., filtered hot to remove a trace of unchanged carbazole, diluted with saturated ethanolic hydrogen chloride (10 c.c.), and cooled. The colourless ***hydrochloride*** which separated had m. p. 233—235° after crystallisation from ethanol (Found: C, 69·4; H, 5·9; N, 13·4. $C_{18}H_{17}N_3$,HCl requires C, 69·35; H, 5·8; N, 13·5%). This hydrochloride is soluble in cold water, unlike the isomer (III; R = H), and gives a ***picrate***, yellow crystals, m. p. 200—202° (immersed at 190°) (from methanol) (Found: C, 57·2; H, 3·8; N, 16·9. $C_{18}H_{17}N_3$,$C_6H_3O_7N_3$ requires C, 56·9; H, 4·0; N, 16·6%).

The infrared spectrum of the hydrochloride showed a band at 3120 cm.$^{-1}$, and a rather broad band at 2840 cm.$^{-1}$, attributed to the $>$NH and $\geqslant$NH$^+$ group respectively.

Indolo(3′ : 2′-1 : 2)carbazole (X).—The hydrochloride (IX) (0·5 g.), when heated to 360°/0·2 mm., gave a colourless sublimate having a pale yellow band at the lower end. The total sublimate, when washed with water, dried (yield 0·3 g., 52%), recrystallised from aqueous ethanol, and resublimed in hydrogen, furnished the indolo-carbazole (X), plates, m. p. 298° (lit.,[6] 299—300°) (Found: C, 83·7; H, 4·7. Calc. for $C_{18}H_{12}N_2$: C, 84·4; H, 4·7%). In benzene solution it showed a strong violet fluorescence in ultraviolet light.

Its ultraviolet spectrum in ethanol showed the characteristics (ε in parentheses): $\lambda_{max.}$ 2630 (40,600), 2830 (35,800), 3200 (9730), 3390 (8750), 3540 (15,180); $\lambda_{min.}$ 2720 (29,900), 3160 (8700), 3310 (4345), 3450 (6160). These values accord well with the curve obtained by Tomlinson [6] for a dioxan solution.

Tetrahydro-4-oxocarbazole Hydrochloride (XI).—When dry hydrogen chloride was passed into a solution of the carbazole in dry ether (in which the carbazole is only moderately soluble), the

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colourless crystalline *hydrochloride* rapidly separated. It was collected, washed with cold ethereal hydrogen chloride, and dried in a calcium chloride desiccator at atmospheric pressure (Found: C, 64·55; H, 5·5; N, 6·5. $C_{12}H_{11}ON$,HCl requires C, 65·0; H, 5·4; N, 6·3%). The salt, when heated from room temperature, had m. p. 220—222°, *i.e.*, that of the oxocarbazole. When immersed at 165°, it partially melted with some effervescence, resolidified, and then melted at 220—222°: when immersed at 200°, complete fusion (with some effervescence) occurred, followed by resolidification and melting as before.

We gratefully acknowledge a grant provided by the Department of Scientific and Industrial Research (to T. J. W.).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 21st*, 1957.]

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306. *Preparation of Cortisol Acetate and 21-Acetoxy-17α-hydroxypregna-4 : 9-diene-3 : 20-dione from 5α-Steroids.*

By R. M. EVANS, G. F. H. GREEN, J. S. HUNT, A. G. LONG, B. MOONEY, and G. H. PHILLIPPS.

4 : 5α-Dihydrocortisone (XII; R = R′ = O; R″ = H) has been reduced to 4 : 5α-dihydrocortisol (XII; R = O; R′ = H, β-OH; R″ = H), the 3- and the 20-keto-group being protected by ketalisation. In the conditions needed for ketalising the 20-keto-group a non-hydroxylic by-product, not hydrolysed to a 20-ketone by acid, is formed.

Acid-catalysed bromination in acetic acid of 4 : 5α-dihydrocortisol 21-acetate or 11β-hydroxyergostan-3-one (II; R = H) yielded 2 : 4-dibromo-Δ^9-compounds, from which ergosta-4 : 9-dien-3-one (XI) and 21-acetoxy-17α-hydroxypregna-4 : 9-diene-3 : 20-dione (XVII) were made. Various esters (II) were tried in attempts to prevent elimination of the 11-hydroxy-group during the halogenation. In ethereal solvents, particularly dioxan, this elimination is prevented, and the 2 : 4-dibromo-compounds can then be converted into cortisol acetate (XIII; R = H, β-OH; R′ = Ac) and 11β-hydroxyergost-4-en-3-one (VIII) respectively.

A PRACTICABLE conversion of 4 : 5α-dihydrocortisone acetate into cortisone acetate has been described in an earlier publication.[1] Attempts to apply such methods to the manufacture of cortisol acetate from 5α-steroids showed that the 11β-hydroxy-group in the intermediate 4 : 5α-dihydrocortisol acetate caused difficulties in the acid-catalysed bromination, as it was readily eliminated with the formation of a Δ^9-steroid. A similar but probably less ready elimination occurs in the Δ^4- and 5β-3-oxo-steroids,[2] and oxidation of the 11β-hydroxy-group has been mentioned as a further undesirable adjunct to the bromination of a 3-oxo-5β-steroid.[3]

In view of the lack of information on the stability of the 11β-hydroxy-3-oxo-5α-steroids in such conditions, we have studied the properties of simple ergostane derivatives obtained from compounds described in an earlier part of our work.[4]

11β-Hydroxy-compounds of this type were converted in acetic acid containing hydrogen bromide into Δ^9-steroids; these products were stable, so that bromination of 11β-hydroxyergostan-3-one (II; R = H), as well as of the Δ^9-ketone (X; X = H), generated 2α : 4α-dibromoergost-9-en-3-one (X; X = Br), which with sodium iodide in acetone and subsequent dehalogenation gave ergosta-4 : 9-dien-3-one (XI). The double bond in ring C is given the 9 : 11-position on the basis of earlier workers' results,[2,5] and the properties

[1] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.
[2] Graber, Haven, and Wendler, *J. Amer. Chem. Soc.*, 1953, **75**, 4722.
[3] Oliveto, Gerold, Weber, Jorgensen, Rausser, and Hershberg, *ibid.*, p. 5486.
[4] Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.
[5] *E.g.*, Shoppee and Reichstein, *Helv. Chim. Acta*, 1943, **26**, 1316, and earlier papers; Heymann and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5938; Bernstein, Lenhard, and Williams, *J. Org. Chem.*, 1954 **19**, 41; Heyl and Herr, *J. Amer. Chem. Soc.*, 1955, **77**, 488.

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of our products support this interpretation. Dehalogenation of the dibromo-compound (X; X = Br) gave ergost-9-en-3-one (X; X = H).

Recent studies with 11β-hydroxy-steroids have shown the unexpected ease with which esters can be made and also that such esters may be more stable in acidic solutions than the free 11β-alcohols. Adapting published methods we have made mono- and di-formates,[6] -acetates,[7] and -trifluoroacetates [8] of ergostane-3β : 11β-diol (I; R = R′ = H), selective esterification and, in the diesters, saponification at the 3-position being possible; however, reaction of ethyl chloroformate [9] with the 11β-hydroxy-group could not be achieved. Selective hydrolysis of the diesters and subsequent oxidation yielded the esters of 11β-hydroxyergostan-3-one (II; R = H); this ketol was also available from the 3β : 11β-diol (I; R = R′ = H) by Oppenauer oxidation.[10a] Except for the acetates, the 11β-esters were not difficult to hydrolyse in conditions that the cortical side-chain might be expected to survive.[11] Although they resemble in this respect the corresponding compounds in the 5β-series, they appear less stable to acidic conditions: for instance, the 11β-formates, although more stable than the 11β-alcohols, are still readily converted into Δ^9-compounds by hydrogen bromide in solvents such as acetic acid and methylene dichloride. Polarimetric evidence suggested that in acetic acid containing hydrogen bromide, or in acetic anhydride and chloroform containing perchloric acid, the 11β-hydroxy-5α-steroids were converted first into 11β-acetates, which then lost the elements of acetic acid.

This inability to exploit esters for our purposes led us to devise conditions for bromination that would curb protonation of the 11β-substituent and so be to the disadvantage of elimination.[12] The desired halogenation (with rearrangement) in ring A is a thermodynamically controlled process in which protons are presumably needed only to unite with the carbonyl group.[13] Directing our efforts at sparing the 11β-hydroxyl group on the basis of such premises, we sought a Lewis base as solvent or additive [14] that would not hinder the halogenation and would not give rise to complications with hydrogen bromide or bromine. In practice ethers,[15] particularly dioxan or diethyl ether, had the desired properties; diphenyl ether was inactive, since resonance detracts from the basic nature of the oxygen atom.[16]

In dioxan 11β-hydroxyergostan-3-one (II; R = H) was brominated to the 2α : 4α-dibromo-ketol (III; X = Br), which gave the 11β-hydroxyergost-4-en-3-one (VIII) by treatment with sodium iodide in acetone and subsequent dehalogenation, or by dehalogenation to the 4-bromo-compound (IV) with subsequent dehydrobromination by means of semicarbazide.[1] Oxidation of the ketol (VIII) gave the unsaturated dione (VII), also derived from ergostane-3 : 11-dione (VI; X = Y = H) by bromination, partial dehydrobromination, and final dehalogenation. Spectroscopic and polarimetric evidence suggests that the bromine atoms at the 2- and the 4-position are equatorially disposed to ring A in the bromo-ketones made in this investigation.[1]

[6] (*a*) Lardon and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 443; (*b*) Oliveto, Gerold, Rausser, and Hershberg, *J. Amer. Chem. Soc.*, 1955, **77**, 3564.

[7] (*a*) Steiger and Reichstein, *Helv. Chim. Acta*, 1937, **20**, 817; (*b*) ref. 3; (*c*) Crawshaw, Henbest, and Jones, *J.*, 1954, 731; (*d*) Kemp, Kappas, Salamon, Herling, and Gallagher, *J. Biol. Chem.*, 1954, **210**, 123.

[8] Cf. Lardon and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 388.

[9] Fieser, Herz, Klohs, Romero, and Utne, *J. Amer. Chem. Soc.*, 1952, **74**, 3309.

[10] (*a*) Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175; (*b*) cf. Rothman and Wall, *J. Amer. Chem. Soc.*, 1957, **79**, 3228.

[11] Callow and James, *J.*, 1956, 4739; ref. 10.

[12] Cf. Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093.

[13] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.

[14] Bell, "Acids and Bases," Methuen and Co. Ltd., London, 1952, p. 30; cf. Glasstone, *Trans. Faraday Soc.*, 1937, **33**, 200; Zellhoeffer, Copley, and Marvel, *J. Amer. Chem. Soc.*, 1938, **60**, 1337.

[15] (*a*) Meerwein and van Emster, *Ber.*, 1922, **55**, 2500; Young, Caserio, and Brandon, *Science*, 1953, **117**, 473; Kosower and Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 4354; (*b*) cf. Hirschmann, Miller, Wood, and Jones, *ibid.*, p. 4956.

[16] Cf. Greenwood and Martin, *Quart. Rev.*, 1954, **8**, 1; Burwell, *Chem. Rev.*, 1954, **54**, 619; Lappert, *ibid.*, 1956, **56**, 1017; Edwards, Gerrard, and Lappert, *J.*, 1957, 348.

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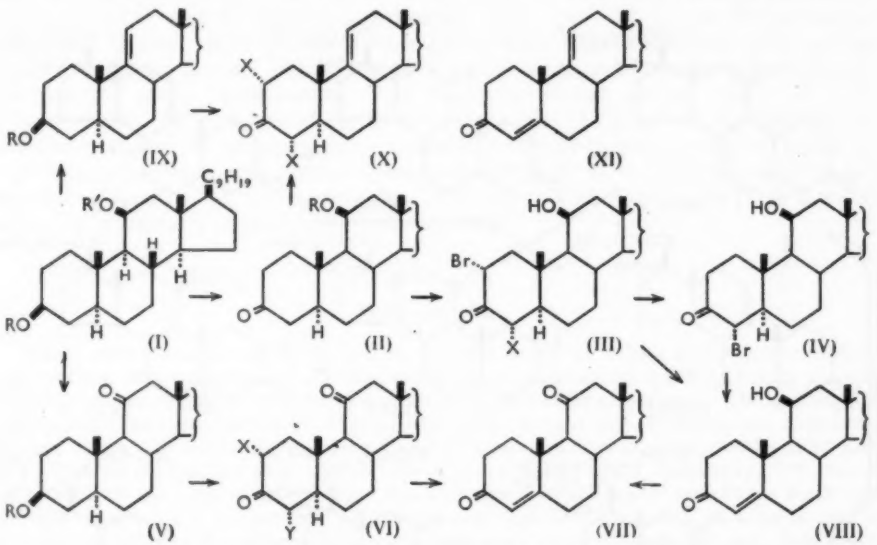
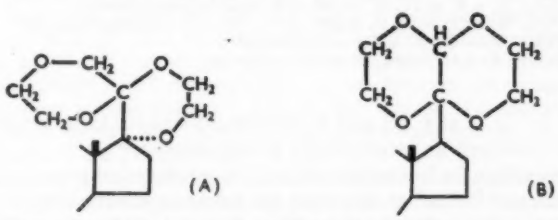
These conversions of Δ^9- and 11β-hydroxy-3-oxo-5α-steroids into Δ^4-3-ketones indicate not only the possibility of new methods for making steroids such as cortisol and the 9-halogeno-corticoids,[17] but also means of avoiding undesirable reactions (particularly halogenation in ring c) that may occur when the 4 : 5-double bond is introduced into 3 : 11 dioxo-steroids. Therefore we continued our studies with these ends in view.

Using dihydrocortisone acetate (XII; R = R′ = O; R″ = Ac) as source, we aimed at making dihydrocortisol acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) by reducing



the 11-oxo-group after protecting the 3- and the 20-keto-group by ketalisation with ethylene glycol.[18] The 3-oxo-group is the more readily ketalised, the 20-oxo-group being affected only after prior hydrolysis of the 21-ester, and then more slowly. Formation of the 20-ketal is accompanied by the generation of a non-hydroxylic compound, whose side-chain is resistant to sodium borohydride and from which the 20-ketone group cannot be



regenerated by mild acid-catalysed hydrolysis.[19] Its stability to acid likens it to the oxetones,[20] sapogenins,[21] and certain sugar anhydrides [22] and distinguishes its behaviour

[17] Ref. 15*b*; Fried and Sabo, *J. Amer. Chem. Soc.*, 1957, **79**, 1130; cf. Barkley, Farrar, Knowles, and Raffelson, *ibid.*, 1954, **76**, 5017; Graber, Snoddy, and Wendler, *Chem. and Ind.*, 1956, 57.

[18] Bernstein, Littell, *et al.*, *J. Org. Chem.*, 1953, **18**, 70; *J. Amer. Chem. Soc.*, 1954, **76**, 6116.

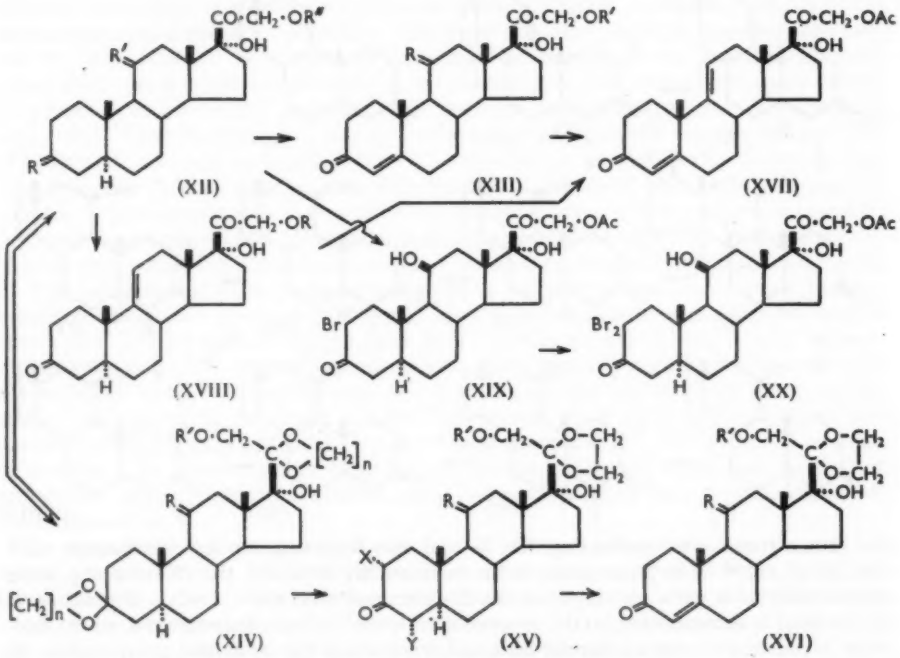
[19] Cf. Levin, Magerlein, McIntosh, Hanze, Fonken, Thompson, Searcy, Scheri, and Gutsell, *ibid.*, p. 546.

[20] Farlow, Burdick, and Adkins, *ibid.*, 1934, **56**, 2498.

[21] Fieser and Fieser, " Natural Products related to Phenanthrene," Reinhold Publ. Corp., New York, 1949, p. 585.

[22] Cf. Haworth and Streight, *Helv. Chim. Acta*, 1932, **15**, 693; Schlubach and Behre, *Annalen*, 1934, **508**, 16; McDonald, *Adv. Carbohydrate Chem.*, 1946, **2**, 253.

from that expected of the ketals of the pregnane-20 : 21-diones;[23] we therefore suppose that it is a spiroketal, *e.g.*, with the system (A), or a tetraoxadecalin[24] derivative (B). However, it did not give acetaldehyde when treated with sulphuric acid and so differs in one respect from many derivatives of dioxan.[25] Unfortunately the generation of such by-products thwarted efficient ketalisation of dihydrocortisone (XII; R = R′ = O; R″ = H), and it could not be improved by the use of trimethylene glycol instead of ethylene glycol. We found that the 3-oxo-group in 4 : 5α-dihydrocortisol and its 21-acetate (XII; R = O;



(XII; R = R′ = O; R″ = H) = 4 : 5α-Dihydrocortisone.
(XII; R = O; R′ = H, β-OH; R″ = H) = 4 : 5α-Dihydrocortisol.
(XIII; R = O; R′ = H) = Cortisone.
(XIII; R = H, β-OH; R′ = H) = Cortisol.

R′ = H, β-OH; R″ = H and Ac) and in cholestan-3-one could be ketalised by means of refluxing methanol without an intentionally added catalyst.[26]

Mild conditions suffice for hydrolysis of the 3 : 3-ethylenedioxy-group, but the 20-ketals survive the conditions[1,18] used in this work for dehydrogenating ring A. Accordingly we have been able to convert the 4-bromo-3-oxo-20-ketal (XV; X = R′ = H; Y = Br; R = O), made by acid-catalysed 2 : 4-dibromination of the 20-ketal (XV; X = Y = R′ = H; R = O) with subsequent partial dehalogenation, into the Δ^4-semicarbazone; reduction of this compound, with subsequent removal of the semicarbazone

[23] Mattox, *J. Amer. Chem. Soc.*, 1952, **74**, 4340; Taub, Pettebone, Wendler, and Tishler, *ibid.*, 1954, **76**, 4094; Mancera, Rosenkranz, and Sondheimer, *ibid.*, 1955, **77**, 5669.
[24] Baker *et al.*, *J.*, 1932, 86; 1933, 1598; Böeseken *et al.*, *Rec. Trav. chim.*, 1935, **54**, 733; 1938, **37**, 133; Jaeger and Smith, *J.*, 1955, 160.
[25] Brown, Calderbank, Johnson, Joshi, Quayle, and Todd, *J.*, 1955, 959.
[26] Cf. Oliveto, Gerold, and Hershberg, *J. Amer. Chem. Soc.*, 1954, **76**, 6113.

group and acetylation, afforded the 20-ketal (XV; X = Y = H; R = H, β-OH; R′ = Ac) of cortisol acetate, albeit in low yield.

Reduction of the bis-ketal (XIV; $n = 2$; R = O; R′ = H) with sodium borohydride and hydrolysis of the product gave 4 : 5α-dihydrocortisol. Its acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) was as unstable in acetic acid containing hydrogen bromide as the behaviour of the simple 11β-hydroxy-5α-steroids foreshadowed, and excellent yields of the Δ⁹-steroid (XVIII; R = Ac) resulted. However, the 11β-alcohol was more stable in dioxan containing hydrogen bromide, and bromination in this solvent yielded crystallisable 2-bromo- (XIX) and 2 : 2-dibromo-compounds (XX), but not a pure 2 : 4-dibromo-compound. Nevertheless, treatment of suitable crude dibromo-products with sodium iodide in refluxing acetone and subsequent dehalogenation gave cortisol acetate, but in disappointing yield. Bromination of 4 : 5α-dihydrocortisol acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) or of the 2-bromo-compound (XIX) in *tert.*-butyl alcohol or with basic catalysis was accompanied by oxidation of the 11-hydroxy-group to 11-ketone.[3]

Dehydrogenation of ring A in the Δ⁹-compound (XVIII; R = Ac) by bromination and dehydrobromination was more successful. The resulting Δ⁴ : ⁹-diene (XVII) is a useful source for biologically active 9-halogeno-compounds.[17]

Experimental

Unless other methods are mentioned, m. p.s were measured with a Kofler block; optical rotations and ultraviolet and infrared absorption pertain to solutions in $CHCl_3$, EtOH, and CS_2 (Nujol for the 5α-pregnane derivatives) respectively, unless otherwise stated. The acid-washed alumina has been described before; [27] other grades were bought from P. Spence and Sons Ltd., Widnes, Lancs. The methods used for infrared spectroscopy have already been described and interpretations of these and the ultraviolet spectra are based on recent compilations.[1, 28] Much information on the infrared absorption of the ergostane derivatives and some of the ketals has been given already; [29] for the rest, the assignments that hold good with an error of only a few $cm.^{-1}$ are C–O in 3β-alcohols (equatorial), 1040 $cm.^{-1}$; in 11β-alcohols (axial), 1030 $cm.^{-1}$ (weaker than the foregoing absorption); in formates, 1180, and in acetates, 1230 $cm.^{-1}$; in ethers (ketals in the pregnane series), 1000—1100 $cm.^{-1}$; C–F, in trifluoroacetates, 1155, 770, and 730 $cm.^{-1}$; C=C, in Δ⁵-steroids, 820 $cm.^{-1}$, and in Δ⁴-3-ketones, 865 $cm.^{-1}$. Weak maxima at 970 and 920 $cm.^{-1}$ may be shown by the formates.[30]

Molecular-rotation Differences.—Consistent changes agreeing with expectation have been noted, except for the conversion of 11β-alcohols into the corresponding Δ⁵-steroids: in two examples, (I; R = R′ = H, β-OH) and (II; R′ = H, β–OH), in the ergostane series the ΔM_D for this change is −16° (±8°), and for the conversion of 4 : 5α-dihydrocortisol acetate (XII; R = O; R′ = H, β–OH; R″ = Ac) $\Delta M_D = -75°$ (and for 11β-hydroxytigogenin and its 3-acetate, $\Delta M_D = -6°$ and −54°, respectively). In the 5β-series the changes are larger, *e.g.*, for 4 : 5β-dihydrocortisol acetate $\Delta M_D = -153°$, as they are for Δ⁴-3-ketones, *e.g.*, for cortisol acetate (XIII; R = H, β-OH; R′ = Ac) −164°, corticosterone acetate −144° (acetone), and 11β-hydroxyergost-4-en-3-one (VIII) −166°.

Using our values for the rotations [see comments after the description herein of ergost-9-en-3β-ol (IX; R = H)], we have corrected the Δ*E* values given by Crawshaw *et al.*[7c] for the introduction of unsaturation between positions 9 and 11, as follows (the figures being given for the 3-alcohol and its acetate respectively): ergostan-3β-ol +20°, +48°; tigogenin +30°, +79°; cholest-9-en-3β-ol +16°, +37°. Acetylation at the 3-position in the Δ⁹-compounds corresponding to the above 5α-steroids is exceptional (but consistent) in giving values of −9°, −6°, and −8° respectively, such esterification usually being accompanied [31] by ΔM_D −34° ± 11°. The 11α-acetoxy-group also conduces to an anomalous change.[19]

[27] Elks, Evans, Long, and Thomas, *J.*, 1954, 451.
[28] Page, *Chem. and Ind.*, 1957, 58.
[29] Page, *J.*, 1955, 2017; Cummins and Page, *J.*, 1957, 3847.
[30] Archer, Lewis, Martini, and Jackman, *J. Amer. Chem. Soc.*, 1954, **76**, 4915.
[31] Ref. 21, p. 208.

Ergostane derivatives.

3β-*Hydroxyergostan*-11-*one* (V; R = H).—The 3β-acetate[30] (V; R = Ac) (7·4 g.) was refluxed for 2·5 hr. with N-potassium hydroxide in methanol (1 l.). The *ketol* (V; R = H) (6·3 g., 93%) separated from hexane as needles, m. p. 161—164°, $[\alpha]_D^{23}$ +43° (c 1·37) (Found: C, 81·0; H, 11·4. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%).

Ergostane-3β : 11β-*diol* (I; R = R′ = H).—3β-Hydroxyergostan-11-one (V; R = H) (12·2 g.) was reduced in 2 hr. in refluxing ethanol (300 ml.) and water (40 ml.) containing sodium borohydride (5·0 g.). Isolation with chloroform afforded the diol named above (10·3 g., 84%), irregular plates (from methanol), m. p. 173—175°, $[\alpha]_D^{20}$ +29°. A recrystallised specimen had m. p. 176—177°, $[\alpha]_D^{25}$ +28° (*c* 1·93) (this compound loses methanol of solvation only slowly) {lit.,[31] m. p. 175—176°, $[\alpha]_D^{20}$ +28°}. Residues from the early crystallisations could be oxidised, giving ergostane-3 : 11-dione (VI; X = Y = H) (1·1 g.).

With acetic anhydride and pyridine the 3β : 11β-diol gave the 3β-acetate (I; R = Ac; R′ = H), rectangular plates (from aqueous acetone), m. p. 131—133°, $[\alpha]_D^{26}$ +20° (*c* 1·52) (Found: C, 78·1; H, 11·2. Calc. for $C_{30}H_{52}O_3$: C, 78·2; H, 11·4%) {lit.,[7c] m. p. 134—135°, $[\alpha]_D^{20}$ +25°}. The 3β-*formate* (I; R = CHO; R′ = H) was made by formylation[6] of the diol (I; R = R′ = H) (1·0 g.) either with acetic–formic anhydride [acetic anhydride (1·35 ml.), 98% formic acid (0·45 ml.), at 0° for 2 hr.] in chloroform (10 ml.) and pyridine (1·8 ml.) for 20 hr., or with 98% formic acid (5 ml.) in pure benzene or ethyl formate (75 ml.), refluxed for 24 hr.; it crystallised from hexane as rods, m. p. 125—128°, $[\alpha]_D^{25}$ +20° (*c* 1·1) [Found: C, 77·7; H, 11·2; CHO, 7·1 (by saponification). $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3; CHO, 6·5%]. This ester was hydrolysed in 2 days at 20° in methanol (80 ml.) and water (10 ml.) containing potassium hydrogen carbonate (2 g.).

The 3β-acetate was also made as follows. The ketol acetate[6] (V; R = Ac) (1·0 g.) was reduced in refluxing tetrahydrofuran (100 ml.) and ethyl acetate (10 ml.) in 3·5 hr. with lithium borohydride (1·0 g.). Careful neutralisation and isolation gave the ester (I; R = Ac; R′ = H) in 86% yield.

11β-*Hydroxyergostan*-3-*one* (II; R = H).—(i) A solution of ergostane-3β : 11β-diol (I; R = R′ = H) (20 g.) in toluene (830 ml.) and *cyclo*hexanone (156 ml.) was distilled to dehydrate it. Aluminium *iso*propoxide (10·4 g.) in anhydrous toluene (104 ml.) was added and the Oppenauer oxidation carried out for 1 hr. in the usual way.[10] The isolated steroid was triturated with light petroleum (b. p. 40—60°; 50 ml.), and the solid *ketol* (II; R = H) (15·2 g., 77%), m. p. 168—174°, $[\alpha]_D^{24}$ +40° (*c* 0·9), filtered off. Crystallisation from methanol gave needles, m. p. 172—174°, $[\alpha]_D^{23}$ +39° (*c* 1·14), giving a precipitate with Brady's reagent (Found: C, 80·9; H, 11·5. $C_{28}H_{48}O_2$ requires C, 80·7; H, 11·6%).

(ii) To a suspension of Raney nickel (20 g.) in sulphur-free toluene (270 ml.) and *cyclo*hexanone (60 ml.) previously refluxed over Raney nickel[32-35] was added the 3 : 11-diol (I; R = R′ = H) (10 g.). The mixture was refluxed for 48 hr. in an anhydrous atmosphere. The steroid obtained after filtration (to remove the nickel) was chromatographed on alumina (Grade H). Light petroleum–ether eluted the ketol (II; R = H), which crystallised from methanol as needles (5 g., 51%), m. p. 171—173°, $[\alpha]_D^{23}$ +40° (*c* 0·7). From ether–chloroform eluates some diol (I; R = R′ = H) (1·98 g.) was recovered.

A solution of the ketol in 0·125N-ethereal hydrogen bromide was stable for at least 0·25 hr.; the ketol could then be recovered efficiently.

3β : 11β-*Diacetoxyergostane* (I; R = R′ = Ac).—The diol (I; R = R′ = H) (5·0 g.) was esterified under nitrogen by acetyl chloride (10 ml.) and *NN*-dimethylaniline (25 ml.) in refluxing benzene (80 ml.) and toluene (40 ml.).[10] The diacetate (I; R = R′ = Ac) (5·33 g., 89%) separated as rods (from methanol), m. p. 117—119°, $[\alpha]_D^{21}$ +30° (*c* 1·06), similar in properties to a specimen described in the literature.[7c] Complete hydrolysis of this diacetate (0·50 g.) occurred in 24 hr. in refluxing 2N-ethanolic potassium hydroxide (50 ml.); with methanolic alkali the conversion was slower.

11β-*Acetoxyergostan*-3β-*ol* (I; R = H; R′ = Ac).—The diacetate (I; R = R′ = Ac) (0·50 g.)

[32] Crawshaw, Henbest, Jones, and Wagland, *J.*, 1955, 3420.
[33] Cf. Kleiderer and Kornfeld, *J. Org. Chem.*, 1948, **13**, 455; Mosettig and Scheer, *ibid.*, 1952, **17**, 764.
[34] Pietro and Traverso, *Gazzetta*, 1952, **82**, 540.
[35] *Org. Synth.*, 1941, **21**, 15.

was hydrolysed for 65 min. in 0·5N-methanolic potassium hydroxide (30 ml.). Two crystallisations of the isolated steroid from methanol yielded the hydroxy-ester (I; R = H; R′ = Ac) (0·18 g.) as needles, m. p. 136—138°, $[\alpha]_D^{24}$ +38° (*c* 0·99) (Found: C, 78·5; H, 11·6. Calc. for $C_{30}H_{52}O_3$: C, 78·2; H, 11·4%). {Crawshaw *et al.*[32] give m. p. 140—141°, $[\alpha]_D^{20}$ +50°, for this compound.}

3β : 11β-*Diformyloxyergostane* (I; R = R′ = CHO).—Chloroform (10 ml.) containing acetic anhydride (5 ml.) was cooled to 0° and " AnalaR " 98—100% formic acid (1·82 ml.) added. The solution was kept at 0° for 2 hr.; the diol (I; R = R′ = H) (0·50 g.) in chloroform (15 ml.) was added, the solution refluxed for 20 hr., and the steroid isolated. The *formate* (I; R = R′ = CHO) (0·30 g.), m. p. 100—101°, $[\alpha]_D^{26}$ +35° (*c* 1·0), crystallised as needles from acetonitrile (Found: C, 76·1; H, 10·6. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·6%). In refluxing methylene dichloride, ether, ethyl bromide, and methyl formate only mono-esterification occurred in the foregoing conditions. An attempt at formylating the diol by means of formic acid and trifluoroacetic anhydride [36] gave a mixture of esters.

The above diformate (0·50 g.) was hydrolysed completely within 2 hr. at 20° in methanol (45 ml.) and water (5 ml.) containing potassium hydroxide (1·4 g.).

11β-*Formyloxyergostan*-3β-*ol* (I; R = H; R′ = CHO).—The diol (I; R = R′ = H) (1·0 g.) was formylated as described above, and the crude product refluxed for 20 hr. in anhydrous methanol (150 ml.). Evaporation of the alcohol and crystallisation of the residue from hexane–acetonitrile and finally aqueous acetone gave the 11-*formate* (I; R = H; R′ = CHO) (0·19 g.) as needles, m. p. 94—100°, 120—131° (capillary tube), $[\alpha]_D^{22}$ +36° (*c* 0·87) (Found: C, 77·7; H, 11·4. $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3%).

Alternatively the 3β : 11β-diformate (I; R = R′ = CHO) (0·5 g.) was hydrolysed in 2 days at 20° to the 11-formate in methanol (150 ml.) and water (20 ml.) containing potassium hydrogen carbonate (2 g.).

3β-*Formyloxyergost*-9-*ene* (IX; R = CHO).—The diol (I; R = R′ = H) (0·5 g.) in 98—100% formic acid (12·5 ml.) and chloroform (5 ml.) was treated at 0° with N-perchloric acid in anhydrous acetic acid (1 ml.). Then acetic anhydride (2 ml.) in chloroform (5 ml.) was added in 0·5 hr. Slight bubbling (probably carbon monoxide) was visible. The solution was left at 0° for 5 hr., then at 20° overnight. The solution was next treated with aqueous sodium acetate, and the steroid crystallised as leaflets (0·37 g.), m. p. 108—110°, from aqueous acetone. The pure specimen of this formate (IX; R = CHO) had m. p. 110—111°, $[\alpha]_D^{23}$ +16° (*c* 1·01), $\lambda_{max.}$ 206 mμ (ε 2910). Yields nearly as good were achieved when perchloric acid was not used in the above type of experiment (cf. ref. 6) (Found: C, 81·1; H, 11·2. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%).

The foregoing ester (0·27 g.) was completely hydrolysed in 24 hr. at 20° with potassium hydrogen carbonate (1 g.) in water (5 ml.) and methanol (100 ml.).

11β-*Formyloxyergostan*-3-*one* (II; R = CHO).—Chloroform (20 ml.), acetic anhydride (10 ml.) and 98% formic acid (3·65 ml.) were kept at 0° for 2 hr. The ketol (II; R = H) (0·50 g.) in chloroform (30 ml.) was added and the mixture refluxed for 20 hr. The isolated steroid, crystallised twice from aqueous acetone, occurred as prisms (0·443 g., 83%), m. p. 143—148°. A pure specimen of the 11-*formate* (II; R = CHO), crystallised from acetonitrile, had m. p. 147—150°, $[\alpha]_D^{22}$ +50° (*c* 1·4) (Found: C, 79·0; H, 11·0. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%).

3β : 11β-*Bistrifluoroacetoxyergostane* (I; R = R′ = CF_3·CO).—The 3 : 11-diol (I; R = R′ = H) (1·0 g.) in pyridine (15 ml.) and chloroform (15 ml.) at −40° was treated with trifluoroacetic anhydride (6 ml.) in chloroform (15 ml.). The solution was set aside for 3 hr. at 20°. The steroidal product crystallised from acetonitrile as prisms (1·18 g., 81%), m. p. 120—123°, $[\alpha]_D^{26}$ +30°, of the *diester* (I; R = R′ = CF_3·CO). The specimen recrystallised for analysis had m. p. 121—123°, $[\alpha]_D^{28}$ +32° (*c* 0·81) (Found: C, 63·1; H, 8·0; F, 18·1. $C_{32}H_{46}O_4F_6$ requires C, 62·9; H, 7·9; F, 18·65%). This ester (1·0 g.) was hydrolysed completely in 3·5 hr. in 0·7N-methanolic sodium hydroxide (40 ml.).

11β-*Trifluoroacetoxyergostan*-3β-*ol* (I; R = H; R′ = CF_3·CO).—The above diester (1·0 g.) in methanol (100 ml.) was stirred during the addition in 12 min. of 0·05N-methanolic sodium hydroxide (35·0 ml., 1·05 equiv.), and then for 15 min. more. The steroid was isolated as a colourless gum (0·79 g.), giving from slightly aqueous acetonitrile crystalline 11-*ester* (I; R = H; R′ = CF_3·CO) (0·28 g.), m. p. 72—82°, 81—93° (capillary tube), $[\alpha]_D^{22}$ +41° (*c* 1·0) (Found: C, 70·1; H, 9·9. $C_{30}H_{46}O_3F_3$ requires C, 70·0; H, 9·6%).

[36] Cf. Bourne, Stacey, Tatlow, *et al.*, *J.*, 1949, 2976; 1954, 2006; *Nature*, 1951, **168**, 942.

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3β-*Trifluoroacetoxyergost*-9-*ene* (IX; R = CF_3·CO).—The 3 : 11-diol (I; R = R′ = H) (1·0 g.) was kept [8] at 20° in trifluoroacetic anhydride (6 ml.) for 2·5 hr. Crystals began to separate after about 0·5 hr. Extraction with ether and crystallisation from acetonitrile, then aqueous acetone, gave rods of the Δ^9-*ester* (IX; R = CF_3·CO) (0·64 g., 54%), m. p. 99—101°, $[\alpha]_D^{26}$ +14° (*c* 0·88), $\lambda_{max.}$ 206 mμ (ε 4190) (Found: C, 72·4; H, 9·7. $C_{36}H_{47}O_2F_3$ requires C, 72·5; H, 9·5%). This ester (0·26 g.) was completely hydrolysed in 17·5 hr. in refluxing 0·7N-methanolic sodium hydroxide (40 ml.).

Ethyl 11β-*Hydroxyergostan*-3β-*yl Carbonate* (I; R = CO_2Et; R′ = H).—To the 3 : 11-diol (I; R = R′ = H) (1·0 g.) in pyridine (15 ml.) ethyl chloroformate (3·0 ml.) was added [9] in 2 min. The temperature rose to 55°; the solution was then heated at 80° for 1·5 hr. Crystallisation from aqueous acetone of the water-precipitated steroid gave the *ester* named above (1·1 g., 95%), m. p. 131—134°. Recrystallisation from acetone afforded laminæ (0·73 g.), m. p. 135—137°, $[\alpha]_D^{26}$ +22° (*c* 1·4), ν 1736, 1260, and 1250 cm.$^{-1}$ (Found: C, 75·9; H, 11·0. $C_{31}H_{54}O_4$ requires C, 75·9; H, 11·1%).

Ergostane-3 : 11-*dione* (VI; X = Y = H).—3β-Hydroxyergostan-11-one (V; R = H) (5·0 g.) in *tert.*-butyl alcohol (100 ml.), water (6 ml.), and pure pyridine (6 ml.) was treated with *N*-bromoacetamide (3 equiv.), the solution being left for 20 hr. under nitrogen at 20°. The isolated *dione* (VI; X = Y = H) (3·5 g., 70%) crystallised from hexane as prisms, m. p. 155—158°, $[\alpha]_D^{25}$ +61° (*c* 1·03) (Found: C, 80·7; H, 11·0. $C_{28}H_{44}O_2$ requires C, 81·1; H, 11·2%). The 3-(2 : 4-*dinitrophenylhydrazone*) formed orange plates (from ethyl acetate), m. p. 249—251° (decomp.), $[\alpha]_D^{20}$ −20° (*c* 0·16), $\lambda_{max.}$ (in $CHCl_3$) 368 mμ (ε 26,500), ν (in Nujol) 1700 cm.$^{-1}$ (Found: N, 9·2. $C_{34}H_{50}O_5N_4$ requires N, 9·4%).

2α-*Bromoergostane*-3 : 11-*dione* (VI; X = Br; Y = H).—The dione (VI; X = Y = H) (1 g.) was dissolved in glacial acetic acid (20 ml.), to which 7N-hydrogen bromide in acetic acid (0·4 ml.) was added. Bromine (0·212 g., 1·1 mol.) in glacial acetic acid was run in as the solution was swirled. The crystals (0·305 g.), m. p. 208—215°, that separated were collected and washed with water and after crystallisation from *cyclo*hexane (yield, 0·178 g.) had m. p. 215—218°, $[\alpha]_D^{20}$ +67° (*c* 1·2) (Found: C, 68·4; H, 9·0; Br, 16·6. $C_{28}H_{43}O_2Br$ requires C, 68·2; H, 9·2; Br, 16·2%). We thank Mr. R. F. K. Meredith for making this bromo-dione.

2α : 4α-*Dibromoergostane*-3 : 11-*dione* (VI; X = Y = Br).—Ergostane-3 : 11-dione (VI; X = Y = H) (2 g.) in anhydrous acetic acid (100 ml.) was treated with 7N-hydrogen bromide in acetic acid (1·5 ml.), then 0·943M-bromine in acetic acid (11·3 ml., 2·2 equiv.) was run in within 2 min., the solution being stirred. Dilution of the solution with water after 35 min. and crystallisation of the precipitate from hexane afforded rods of the 2 : 4-*dibromo-ketone* (1·57 g.; 57%), m. p. 153—156° (decomp.), $[\alpha]_D^{23}$ +38° (*c* 1·62) (Found: Br, 28·0. $C_{28}H_{44}O_2Br_2$ requires Br, 27·9%).

Ergost-4-*ene*-3 : 11-*dione* (VII).—(i) The 2 : 4-dibromo-ketone (VI; X = Y = Br) (10·0 g.) was treated with sodium iodide (5 g.) and bromoacetone in acetone (200 ml.) as described earlier.[1] The product, after dehalogenation, was chromatographed on alumina (Grade O); the benzene eluates crystallised from slightly aqueous acetonitrile, giving plates of the *ene-dione* (VII) (3·1 g., 43%), m. p. 119—122°, $[\alpha]_D^{23}$ +166°, $\lambda_{max.}$ 237·5 mμ (ε 15,400). The purest sample, plates from methanol or acetonitrile, had m. p. 120—124°, $[\alpha]_D^{26}$ +165° (*c* 1·05), $\lambda_{max.}$ 238 mμ (ε 15,400) (Found: C, 81·4; H, 10·95. $C_{28}H_{44}O_2$ requires C, 81·5; H, 10·8%). The 3-(2 : 4-*dinitrophenylhydrazone*), yellow needles, had m. p. 234—237°, $[\alpha]_D^{20}$ +400° (*c* 0·4), $\lambda_{max.}$ 389 mμ (ε 30,240), ν (in Nujol) 1703 cm.$^{-1}$ (Found: C, 69·2; H, 7·9; N, 9·5. $C_{34}H_{48}O_5N_4$ requires C, 68·9; H, 8·2; N, 9·5%).

(ii) 11β-Hydroxyergost-4-en-3-one (VIII) (0·48 g.) in "AnalaR" acetone (50 ml.) was oxidised [10,37] in 1 min. with 1·33N-potassium dichromate in 5N-sulphuric acid (2·30 ml.). The crude product (0·46 g.), m. p. 105—112°, was purified as described above, to give the pure dione (VII) (0·23 g., 49%).

2α-*Bromo*-11β-*hydroxyergostan*-3-*one* (III; X = H).—The ketol (II; R = H) (3 g.) in pure dioxan (125 ml.) was treated at 20° with bromine (1·24 g., 1·08 equiv.) in 1 min. The solution was kept for another 0·5 min., then diluted with aqueous sodium hydrogen carbonate. Rapid crystallisation of the precipitate from hexane gave plates of the 2α-*bromo-ketone* (III; X = H) (2·54 g., 71%), m. p. 140—151°, slow crystallisation of which gave needles (2·24 g., 63%), m. p. 174—177°, $[\alpha]_D^{23}$ +48° (*c* 1·0) (Found: C, 68·0; H, 9·4; Br, 15·7. $C_{28}H_{47}O_2Br$ requires

[37] Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547.

C, 67·9; H, 9·6; Br, 16·1%). Spectra of the higher-melting form showed evidence of hydrogen-bonding in Nujol mulls. Rapid crystallisation converted it into the plates.

2α : 4α-*Dibromo*-11β-*hydroxyergostan*-3-*one* (III; X = Br).—The ketol (II; R = H) (5 g.) in pure dioxan (197 ml.) at 12° was treated with a drop of 4N-hydrogen bromide in dioxan, and then bromine (3·93 g., 2·05 mol.) was added in 2 min. The solution was kept at 20° for 80 min. (by which time the rotation had stopped decreasing). The isolated steroid crystallised from ethanol, giving the 2α : 4α-*dibromo-ketone* (III; X = Br) (3·82 g., 56%), m. p. 192—200° (decomp.). Recrystallisation afforded needles (2·11 g., 33%), m. p. 213—214° (decomp.), $[\alpha]_D^{23}$ +12°. The analytical specimen had m. p. 210—212° (decomp.), $[\alpha]_D^{22}$ +10° (*c* 0·4) (Found: C, 58·5; H, 8·1; Br, 26·7. $C_{28}H_{46}O_2Br_2$ requires C, 58·6; H, 8·1; Br, 27·8%).

4α-*Bromo*-11β-*hydroxyergostan*-3-*one* (IV).—The crude 2 : 4-dibromo-compound (III; X = Br) (3·01 g.) in acetic acid (70 ml.) and methylene dichloride (25 ml.) was stirred vigorously and treated at 20° under carbon dioxide with 1·64N-chromous chloride (5·76 ml.) through a capillary jet during 1·6 hr.[1] Isolation of the steroid with methylene chloride afforded a residue (2·43 g.), $[\alpha]_D^{20}$ +21° (*c* 1·0) (Found: Br, 16·0%); trituration with acetone and filtration afforded the 4α-*bromo-ketone* (IV) (0·48 g., 14%), m. p. 173—177°, $[\alpha]_D^{21}$ +2°. Recrystallisation from methanol–ether gave the pure compound as plates (0·39 g., 11%), m. p. 170—173°, $[\alpha]_D^{25}$ −2° (*c* 1·0) (Found: C, 68·0; H, 9·7; Br, 15·65. $C_{28}H_{47}O_2Br$ requires C, 67·9; H, 9·6; Br, 16·1%).

11β-*Hydroxyergost*-4-*en*-3-*one* (VIII).—(i) The 2 : 4-dibromo-ketone (III; X = Br) (2·31 g.) was treated with sodium iodide (11·6 g.) in acetone (70 ml.) containing bromoacetone, as described earlier.[1] Dehalogenation (with chromous chloride) of the product and isolation gave the crude steroid (1·80 g.), $[\alpha]_D^{20}$ +85°. Four crystallisations from acetone gave rhombs of product (VIII) (0·75 g., 49%), m. p. 169—173°, $[\alpha]_D^{20}$ +106° (*c* 0·9), $\lambda_{max.}$ 241 mμ (ε 15,100) (Found: C, 81·3; H, 11·1. $C_{28}H_{46}O_2$ requires C, 81·1; H, 11·2%).

(ii) The 4-bromo-ketone (IV) (0·25 g.) was dehydrobrominated with semicarbazide.[1] The crude product (VIII) (0·195 g., 93%), m. p. 167—172°, obtained by decomposition of the semicarbazone, crystallised from acetone, giving the pure compound (0·175 g., 84%).

2α : 4α-*Dibromoergost*-9-*en*-3-*one* (X; X = Br).—(i) The ketol (II; R = H) (1 g.) in pure dioxan (20 ml.) at 10° was treated with 5·3N-hydrogen bromide in dioxan (3·56 ml.) and then with bromine (0·272 ml., 2·2 mole) dropwise with stirring. The solution (N with respect to hydrogen bromide) was kept at 20° for 18 min., diluted with sodium acetate solution, and extracted with ether. The isolated steroid (1·6 g.) was crystallised four times from ethanol, giving needles of the pure Δ⁹-*ketone* (X; X = Br) (0·20 g., 14%), m. p. 220—220·5° (decomp.), $[\alpha]_D^{25}$ +2° (*c* 0·92) (Found: C, 60·6; H, 8·0; Br, 27·7. $C_{28}H_{44}OBr_2$ requires C, 60·4; H, 8·0; Br, 28·7%).

(ii) The enone (X; X = H) (1 g.), stirred in acetic acid (50 ml.) to which 5·6N-hydrogen bromide in acetic acid had been added, was brominated with 0·90M-bromine in acetic acid (9·8 ml., 2·2 equiv.). A pale yellow colour remained after 3 min. and crystallisation began. The mixture was stirred for 75 min. in all, and the crystals (1·12 g., 80%), m. p. 203° (decomp.; capillary tube), were then collected and washed. Crystallisation from ethyl acetate gave needles of the pure ketone (X; X = Br) (0·82 g.), m. p. 216° (decomp.; capillary tube), with a second crop (0·22 g., total 75%), m. p. 212° (decomp.; capillary tube). A recrystallised specimen for analysis had m. p. 222° (decomp.), $[\alpha]_D^{24}$ +2° (*c* 1·6), $\lambda_{max.}$ 210 (ε 3500) and 206 mμ (ε 3360) (Found: C, 60·3; H, 8·0; Br, 28·5%).

The above dibromo-compound (472 mg.) in chloroform (20 ml.) and acetic acid (10 ml.) was stirred under nitrogen at 20° for 1 hr. with acid-washed zinc dust (2 g.). Filtration, isolation of the steroid from the filtrate, and crystallisation afforded ergost-9-en-3-one (X; X = H) (237 mg., 70%).

Ease of Conversion of Ergostane-3β : 11β-*diol and its Acetates into* Δ⁹-*Steroids*.—The diol (I; R = R′ = H), diacetate (I; R = R′ = Ac), and 3-acetate (I; R = Ac; R′ = H) were dissolved severally (100 mg. each) in chloroform (12 ml.) containing acetic anhydride (2·4 ml.). 60% Perchloric acid (0·5 ml.) was added to acetic anhydride (10 ml.) with cooling, and part (1·6 ml.) of the solution was added to each of the steroid solutions. The rotation of the diol increased just perceptibly for 2 min., then fell to $[\alpha]_D$ +11° in 35 min., darkening the while; with the diacetate the rotation fell evenly from $[\alpha]_D$ +29° to a steady +12° in 60 min., and the solution darkened; with the 3-acetate $[\alpha]_D$ +20° → 31° in 1·5 min., then reached constant $[\alpha]_D$ +16° in 24 min. (In each case the rotations were calculated from the weight of starting

material.) Each experiment afforded 3β-acetoxyergost-9-ene (IX; R = Ac) in 70% yield after addition of potassium acetate and isolation and crystallisation of the steroid.

An attempt at isolating the diacetate after 1·5 minutes' treatment of the 3-acetate gave a mixture containing (by infrared and polarimetric analysis) about 80% of the former and 20% of the Δ^9-ester (IX; R = Ac).

Ergost-9-en-3β-ol (IX; R = H).—The 3 : 11-diol (I; R = R′ = H) (10·0 g.) in chloroform (150 ml.) and acetic anhydride (30 ml.) was treated with acetic anhydride (20 ml.) to which " AnalaR " 60% w/w perchloric acid (1·0 ml.) had been added. The solution became warm and darkened. After 45 min. it was diluted with aqueous potassium acetate, and the steroid isolated and hydrolysed in 1 hr. with potassium hydroxide (24 g.) in ethanol (600 ml.). The water-precipitated product (8·0 g., 84%), m. p. 147—150°, crystallised from methanol as rhombs of the enol (IX; R = H), m. p. 148—149°, $[\alpha]_D^{23}$ +21° (*c* 0·93), $\lambda_{max.}$ 205 mμ (ε 3600) (Found: C, 83·8; H, 12·1. Calc. for $C_{28}H_{48}O$: C, 83·9; H, 12·1%). Crawshaw *et al.*[7c] give m. p. 147·5—149°, $[\alpha]_D$ +29°, for this compound, but in a letter to us Dr. Henbest writes that their pure material has m. p. 152—153°, $[\alpha]_D$ +19°. The 3β-acetate (IX; R = Ac), crystallised from methanol and aqueous acetone, had m. p. 127—129°, $[\alpha]_D^{27}$ +17° (*c* 1·76), $\lambda_{max.}$ 203 mμ (ε 4290) (Found: C, 81·5; H, 11·5. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·4% {lit.,[7c,32] m. p. 128—132°, $[\alpha]_D$ +17°}.

Ergost-9-en-3-one (X; X = H).—(i) The enol (IX; R = H) (8·0 g.) in refluxing " AnalaR " acetone (400 ml.) was oxidised with 0·33M-potassium dichromate in 4N-sulphuric acid (26 ml.) added quickly;[10,27] after the solution had been stirred for another 2·5 min., the excessive oxidant was destroyed with sodium pyrosulphite. The water-precipitated *enone* (X; X = H) crystallised from aqueous acetone (charcoal) as hexagonal plates (6·75 g.; 85%), m. p. 151—153°. Recrystallised material had m. p. 153—155°, $[\alpha]_D^{25}$ +39° (*c* 1·24), $\lambda_{max.}$ 204 mμ (ε 4550) (Found: C, 84·2; H, 11·5. $C_{28}H_{46}O$ requires C, 84·4; H, 11·6%).

(ii) A solution of 11β-hydroxyergostan-3-one (II; R = H) (2 g.) in pure acetic acid (45 ml.) was treated with 6·5N-hydrogen bromide in acetic acid (8 ml.). After 15 min. aqueous sodium acetate was added and the precipitated steroid crystallised twice (from acetone and hexane), to give the enone (X; X = H) (0·05 g.), m. p. 150—152°.

Stability of the 3 : 11-*Diesters in Solvents containing Hydrogen Bromide.*—In 0·65N-hydrogen bromide in acetic acid the formate (I; R = R′ = CHO) and acetate (I; R = R′ = Ac) decomposed within a few min., the rotation tending negativewards. Pure products could not be isolated. The trifluoroacetate (I; R = R′ = CF_3·CO) was stable and recovered in 63% yield after 3 hours' treatment. All the esters withstood 0·65N-hydrogen bromide in dioxan more effectively and were recoverable in >40% yield after 0·5 hr. The diacetate was stable in 2% (v/v) ethanolic methylene dichloride made 0·13N in hydrogen bromide, from which it could be recovered in 54% yield. See method (ii) for making ergost-9-en-3-one (X; X = H).

*Ergosta-*4 : 9-*dien-3-one* (XI).—2α : 4α-Dibromoergost-9-en-3-one (X; X = Br) (210 mg.) was treated with sodium iodide (1·06 g.) in acetone (31 ml.), as previously described.[1] Dehalogenation and extraction with methylene dichloride gave a gum (160 mg.), crystallising satisfactorily after elution with ether from alumina. This solid (146 mg.) had $\lambda_{max.}$ 238 mμ ($E_{1cm.}^{1\%}$ 374). Two further crystallisations from acetonitrile yielded laminæ of the *dienone* (XI) (74 mg., 49%), m. p. 107—109°, $[\alpha]_D^{24}$ +69° (*c* 0·8), $\lambda_{max.}$ 239 mμ (ε 15,600) (Found: C, 85·0; H, 11·2. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%).

5α-*Pregnane derivatives*

4 : 5α-*Dihydrocortisone* (XII; R = R′ = O; R″ = H).—The 21-acetate (XII; R = R′ = O; R″ = Ac) (50 g.), suspended in refluxing methanol (1 l.), was stirred while M-potassium hydrogen carbonate (136 ml., 1·1 equiv.) was added[38] during 1·5 min. Heating and stirring were continued for another 15·5 min., and the solution cooled and neutralised cautiously with glacial acetic acid. Concentration afforded a slurry, from which the *alcohol* (XII; R = R′ = O; R″ = H) (45·3 g.) was obtained by extraction with methylene dichloride. This material, m. p. 196—205°, $[\alpha]_D^{22}$ +74°, was good enough for most purposes; successive crystallisations from methanol and acetone afforded the pure compound as needles, m. p. 217—221° (decomp.), $[\alpha]_D^{23}$ +78° (*c* 0·4), +78° (*c* 0·5 in acetone), +81° (*c* 1·0 in dioxan), +90° (*c* 1·0 in EtOH or MeOH), ν 1706 cm.$^{-1}$ (Found: C, 69·4; H, 8·3. $C_{21}H_{30}O_5$ requires C, 69·6; H, 8·3%).

[38] Cf. Reichstein and von Euw, *Helv. Chim. Acta*, 1938, **21**, 1181.

A sample of this compound described [39] with m. p. 229—233°, $[\alpha]_D^{24}$ +100°, may be the 21-acetate. Sondheimer, Batres, and Rosenkranz [39a] give m. p. 208—210°, $[\alpha]_D$ +78°, for the 21-alcohol.

Acid-catalysed hydrolysis was less efficient.[40]

17α : 21-*Dihydroxy*-3 : 3-*dimethoxy*-5α-*pregnane*-11 : 20-*dione* [XII; R = $(OMe)_2$; R′ = O; R″ = H].—4 : 5α-Dihydrocortisone (XII; R = R′ = O; R″ = H) (18·2 g.) dissolved in refluxing anhydrous methanol and yielded, on cooling, the 3 : 3-*dimethoxy-compound* (14·4 g., 64%), m. p. 172—175°, $[\alpha]_D^{22}$ +53°. The recrystallised ketal separated as needles (8·6 g., 38%), m. p. 177—181°, $[\alpha]_D^{23}$ +52° (*c* 1·1), ν 1701 and 1101 cm.$^{-1}$ (Found: C, 67·9; H, 8·9. $C_{23}H_{36}O_6$ requires C, 67·6; H, 8·9%). The 21-*acetate* [XII; R = $(OMe)_2$; R′ = O; R″ = Ac], made with acetic anhydride and pyridine or from 4 : 5α-dihydrocortisone acetate (XII; R = R′ = O; R″ = Ac) by ketalisation in the above manner, crystallised from methanol containing a trace of pyridine as plates, m. p. 205—212°, $[\alpha]_D^{22}$ +87° (*c* 0·6), ν (in $CHCl_3$) 1748, 1728, and 1708, and 1100 cm.$^{-1}$ (the spectrum of a Nujol mull gave anomalous bands in the 1725—1740 cm.$^{-1}$ region) (Found: C, 67·0; H, 8·5. $C_{25}H_{38}O_7$ requires C, 66·65; H, 8·5%).

The 3 : 3-dimethoxy-21-alcohol [XII; R = $(OMe)_2$; R′ = O; R″ = H] (1 g.) gave the 3-ketone (XII; R = R′ = O; R″ = H) (0·55 g.) by hydrolysis with acetone (45 ml.), water (5 ml.) and 2N-hydrochloric acid for 1·5 hr. at room temperature.[18]

Cholestan-3-one also formed a ketal in the foregoing conditions. However it was best made by the following method.

3 : 3-*Dimethoxycholestane*.—Cholestan-3-one (0·50 g.) was refluxed in anhydrous methanol (50 ml.) with anhydrous oxalic acid (10 mg.) for 3 hr.; the solution was then evaporated under reduced pressure to small bulk. A solid (0·53 g.), m. p. 77—79°, crystallised slowly. It was recrystallised from methanol with methylene dichloride or *tert.*-butyl alcohol (with a trace of pyridine) as a mixture of blades and needles of 3 : 3-*dimethoxycholestane*, m. p. 79—80°, $[\alpha]_D^{24}$ +23° (*c* 0·84 in 99 : 1 $CHCl_3$–pyridine) (Found: C, 80·65; H, 12·0. $C_{29}H_{52}O_2$ requires C, 80·5; H, 12·1%).

3 : 3-*Ethylenedioxy*-17α : 21-*dihydroxy*-5α-*pregnane*-11 : 20-*dione* (XII; R = O·CH_2·CH_2·O; R′ = O; R″ = H) *and the Formation of a Non-hydroxylic Ketal*.—4 : 5α-Dihydrocortisone (XII; R = R′ = O; R″ = H) (17·9 g.) was heated for 5 hr. in refluxing benzene (650 ml.) and ethylene glycol (140 ml.) containing toluene-*p*-sulphonic acid monohydrate (0·54 g.), the evolved water being separated from the azeotrope.[18] The steroidal product was separated into benzene-soluble and -insoluble fractions, the latter crystallising from acetone as rhombs of the 3-ketal (XII; R = O·CH_2·CH_2·O; R′ = O; R″ = H) (0·42 g.), m. p. 208—213°, $[\alpha]_D^{20}$ +53° (*c* 1·1), ν 1720, 1705, 1100, and 1060 cm.$^{-1}$ (Found: C, 68·1; H, 8·45. $C_{23}H_{34}O_6$ requires C, 67·95; H, 8·4%). The 21-*acetate* (XII; R = O·CH_2·CH_2·O; R′ = O; R″ = Ac), made from the above (0·2 g.) with pyridine (5 ml.) and acetic anhydride (2·5 ml.), crystallised from acetone as rods (0·19 g.), m. p. 280—281°, $[\alpha]_D^{20}$ +82° (*c* 0·85), ν 1752, 1232, 1728, 1708, 1105, and 1062 cm.$^{-1}$ (Found: C, 67·1; H, 7·9. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·1%).

The benzene-soluble fraction from the ketalisation was isolated as a gum, part of which crystallised from acetone–hexane and then from acetone as the bisketal (XIV; n = 2; R = O; R′ = H) (3·13 g.), m. p. 184—186°, $[\alpha]_D^{20}$ +36° (see below). Concentration of the mother-liquors afforded a non-hydroxylic 3-*ketal* (1·0 g.), m. p. 219—221° (from acetone), $[\alpha]_D^{20}$ +25°. Recrystallisation afforded this compound, m. p. 223—225°, $[\alpha]_D^{20}$ +29° (*c* 1·0), ν (in CS_2) 1710 and 1100 cm.$^{-1}$ but no hydroxyl bands (Found: C, 68·3; H, 8·3. $C_{27}H_{40}O_7$ requires C, 68·0; H, 8·5%).

Properties of the foregoing ketal $C_{27}H_{40}O_7$. The compound (0·5 g.) was treated [18] for 27 hr. at room temperature with acetone (40 ml.), water (4·5 ml.), and 2N-hydrochloric acid (0·375 ml.). The filtered solution was diluted with water, and the precipitate (0·48 g.), m. p. 260—266° (decomp.), crystallised from methanol as plates of a non-hydroxylic 3 : 11-*dioxo-compound* (0·33 g.), m. p. 263—268° (decomp.), $[\alpha]_D^{22}$ +47° (*c* 0·9), ν (in CS_2) 1710, 1118, and 1102 cm.$^{-1}$ (Found: C, 69·6; H, 8·4. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%).

Attempted hydrolysis with 8·5% aqueous sulphuric acid in methanol [18] gave no recognisable product.

The ketal (1 g.) was reduced in 2 hr. in refluxing ethanol (90 ml.) and water (15 ml.) containing

[39] Chemerda, Chamberlin, Wilson, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 4052.
[39a] Sondheimer, Batres, and Rosenkranz, *J. Org. Chem.*, 1957, **22**, 1090.
[40] Mattox and Kendall, *J. Biol. Chem.*, 1951, **188**, 287; cf. Edwards and Kellie, *Biochem. J.*, 1954, **56**, 207.

XUM

sodium borohydride (1 g.). Addition of water precipitated an 11β-*hydroxy-compound* (0·86 g.), m. p. 262—264°, $[\alpha]_D^{23}$ +29° (*c* 1·1), ν 1095 cm.$^{-1}$ (Found: C, 67·8; H, 9·2. $C_{27}H_{42}O_7$ requires C, 67·75; H, 8·85%).

None of the compounds mentioned in this section gave a colour with alkaline triphenyltetrazolium solutions.[41]

3 : 3-20 : 20-*Bisethylenedioxy*-17α : 21-*dihydroxy*-5α-*pregnan*-11-*one* (XIV; n = 2; R = O; R′ = H).—A suspension of 4 : 5α-dihydrocortisone (XII; R = R′ = O; R″ = H) (45·3 g.) in ethylene glycol (550 ml.) containing toluene-*p*-sulphonic acid hydrate (0·192 g.) was refluxed at 100—110°/16—20 mm. with an air-condenser and nitrogen leak [18] for 4·5 hr. The product was poured into water (3 l.) containing a little sodium hydrogen carbonate, and the steroid extracted with methylene dichloride. Crystallisation from ether gave the 3 : 3-20 : 20-*bis-ketal* (XIV; n = 2; R = O; R′ = H) (36 g., 64%), m. p. 176—182°, $[\alpha]_D^{22}$ +34°. The analytical specimen crystallised from acetone as needles, m. p. 184—186°, $[\alpha]_D^{20}$ +36° (*c* 1·0), ν 1680, 1052, and 1100 cm.$^{-1}$ (Found: C, 66·7; H, 8·4. $C_{25}H_{38}O_7$ requires C, 66·6; H, 8·5%). The yields were always lower when the two-phase benzene–ethylene glycol ketalisations [18] were tried. The 21-*acetate* (XIV; n = 2; R = O; R′ = Ac), made from the foregoing bisketal (0·5 g.) in pyridine (3 ml.) and acetic anhydride (1·5 ml.) overnight at room temperature, occurred as flat needles (from acetone–hexane), m. p. 197—200°, $[\alpha]_D^{22}$ +35° (*c* 1·0), ν 1750, 1230, 1690, 1186, 1095, and 1044 cm.$^{-1}$ (Found: C, 65·75; H, 8·1. $C_{27}H_{40}O_8$ requires C, 65·8; H, 8·2%).

17α : 21-*Dihydroxy*-3 : 3-20 : 20-*bis*(*trimethylenedioxy*)-5α-*pregnan*-11-*one* (XIV; n = 3; R = O; R′ = H).—4 : 5α-Dihydrocortisone (XII; R = R′ = O; R″ = H) (1 g.), benzene (36 ml.), redistilled trimethylenediol (10 ml.), and toluene-*p*-sulphonic acid (11 mg.) were heated under reflux for 20 hr. with azeotropic removal of water. Dilution with sodium hydrogen carbonate solution and extraction with methylene dichloride, and crystallisation of the product from ether and twice from acetone, gave the 3 : 3-20 : 20-*bisketal* (0·45 g., 27%), m. p. 215—219°, $[\alpha]_D^{19}$ +47° (*c* 1·0), ν 1708 and 1102 cm.$^{-1}$ (Found: C, 67·7; H, 8·6. $C_{27}H_{42}O_7$ requires C, 67·75; H, 8·85%).

20 : 20-*Ethylenedioxy*-17α : 21-*dihydroxy*-5α-*pregnane*-3 : 11-*dione* (XV; R = O; R′ = X = Y = H).—A solution of the bisketal (XIV; n = 2; R = O; R′ = H) (0·5 g.) in acetone (20 ml.) and water (3 ml.) was treated [18] with 2N-hydrochloric acid (0·25 ml.). The optical rotation of the solution was constant within 21 hr., and extraction of the steroid with methylene dichloride afforded the 3-*oxo-ketal* named above, crystallising from acetone as rods (0·31 g., 70%), m. p. 223—226°, $[\alpha]_D^{22}$ +57° (*c* 1·0), ν 1710 and 1684 cm.$^{-1}$ (Found: C, 68·15; H, 8·5. $C_{23}H_{34}O_6$ requires C, 67·95; H, 8·4%). Its 21-*acetate*, made in the usual manner, crystallised from acetone as plates, m. p. 246—250°, $[\alpha]_D^{22}$ +54° (*c* 0·8), ν 1744, 1234, and 1708 cm.$^{-1}$ (Found: C, 67·2; H, 8·0. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·1%). Hydrolysis [18] of the 3-ketal group in the bisketal was achieved in 75% yield in 50% (v/v) aqueous acetic acid at 70° for 0·5 hr.

The above 20-ketals gave no colour with alkaline triphenyltetrazolium solutions.[41] Although the rotations of their solutions in acetic acid or chloroform containing hydrogen bromide hardly changed, no pure steroid could be recovered therefrom.

3 : 3-20 : 20-*Bisethylenedioxy*-5α-*pregnane*-11β : 17α : 21-*triol* (XIV; n = 2; R = H, β-OH; R′ = H).—Sodium borohydride (1·2 g.) was added to a solution of the 11-oxo-bisketal (XIV; n = 2; R = O; R′ = H) (1·5 g.) in methanol (26 ml.) and water (5 ml.), which was then refluxed for 6 hr. Crystallisation from acetone of the steroid extracted with methylene dichloride gave the 11β-*hydroxy-bisketal* (1·0 g., 67%) as rods, m. p. 228—231°, $[\alpha]_D^{21}$ +19° (*c* 1·0), ν 1185 and 1100 cm.$^{-1}$ (Found: C, 66·6; H, 9·2. $C_{25}H_{40}O_7$ requires C, 66·35; H, 8·9%). Its 21-*acetate* was eluted from alumina (Grade H) with ether and crystallised from acetone–*cyclo*hexane as rhombs, m. p. 152—155°, $[\alpha]_D^{24}$ +18° (*c* 1·3), ν 1740, 1232, and 1095 cm.$^{-1}$ (Found: C, 65·8; H, 8·75. $C_{27}H_{42}O_8$ requires C, 65·6; H, 8·6%). (Some 11β-esterification may have accompanied the desired acetylation [7]; see below.)

11β-*Acetoxy*-3 : 3-20 : 20-*bisethylenedioxy*-5α-*pregnane*-17 : 21-*diol* (XIV; n = 2; R = H, β-OAc; R′ = H).—Toluene (8 ml.), *NN*-dimethylaniline (10 ml.), and acetyl chloride (2 ml.) were added to a solution of the bisketal (XIV; n = 2; R = H, β-OH; R′ = H) (1 g.) in benzene (16 ml.). The mixture was refluxed under nitrogen [7, 19] for 20 hr., then cooled; the steroid (1·17 g.), isolated with ether, was hydrolysed at the 21-position in 50 min. in refluxing methanol (15 ml.) and water (10 ml.) containing potassium hydrogen carbonate (0·7 g.).[38] Precipitation and crystallisation from methanol gave the 11β-*acetate* (0·77 g., 71%) as plates,

[41] Zaffaroni, *Recent Progr. Hormone Res.*, 1953, **8**, 77.

m. p. 160—163°, $[\alpha]_D^{20}$ +32° (*c* 0·84), ν 1734, 1250, and 1098 cm.$^{-1}$ (Found: C, 65·5; H, 8·3. $C_{27}H_{42}O_6$ requires C, 65·6; H, 8·6%).

The 11β : 21-*diacetate* (XIV; n = 2; R = H, β-OAc; R′ = Ac), made by simple acetylation of the above, formed solvated plates (from hexane), m. p. 115—120° (after losing solvent at 95—105°). Recrystallisation from carbon tetrachloride, then from light petroleum, and finally heating the crystals at 80°/0·1 mm. for 3 hr. gave the pure ester, m. p. 115—120°, $[\alpha]_D^{22}$ +31° (*c* 1·0), ν (in CS_2) 1750 and 1240 (21-acetate), 1730 and 1240 (11-acetate), and 1095 cm.$^{-1}$ (Found: C, 64·9; H, 8·3. $C_{29}H_{44}O_8$ requires C, 64·9; H, 8·3%).

20 : 20-*Ethylenedioxy*-11β : 17α : 21-*trihydroxy*-5α-*pregnan*-3-*one* (XV; R = H, β-OH; R′ = X = Y = H).—The bisketal (XIV; n = 2; R = H, β-OH; R′ = H) (0·58 g.) was hydrolysed at the 3-position with acetone (24 ml.), water (3·5 ml.), and 2N-hydrochloric acid (0·29 ml.) as described [18] for this purpose. The 20-*ketal* (XV; R = H, β-OH; R′ = X = Y = H) (0·25 g., 48%) crystallised from acetone as needles, m. p. 225—226°; recrystallised material had m. p. 228—230°, $[\alpha]_D^{21}$ +29° (*c* 0·85), ν 1708 and 1072 cm.$^{-1}$ (Found: C, 67·6; H, 9·0. $C_{23}H_{36}O_6$ requires C, 67·6; H, 8·9%). Its 21-*acetate* formed rhombs (from methanol), m. p. 245—251°, $[\alpha]_D^{20}$ +24° (*c* 0·7), ν 1735 and 1255, and 1708 cm.$^{-1}$ (Found: C, 66·45; H, 8·5. $C_{25}H_{38}O_7$ requires C, 66·6; H, 8·5%).

4 : 5α-*Dihydrocortisol* (XII; R = O; R′ = H, β-OH; R″ = H).—A solution of the bisketal (XIV; R = H, β-OH; R′ = H) (27 g.) in methanol (500 ml.) and 8·5% (v/v) sulphuric acid (50 ml.) was refluxed [18] for 1 hr. Isolation of the steroid with ethyl acetate and crystallisation therefrom yielded the *ketol* (XII; R = O; R′ = H, β-OH; R″ = H) (16·03 g., 74%), m. p. 234—240° (decomp.), $[\alpha]_D^{24}$ +67° (in dioxan); recrystallisation from acetone gave a specimen, m. p. 230—240° (decomp.), $[\alpha]_D^{21}$ +66° (*c* 1·1; dioxan), ν 1703 and 1692 cm.$^{-1}$ (Found: C, 69·5; H, 9·0. $C_{21}H_{32}O_5$ requires C, 69·2; H, 8·85%). Acetylation afforded the 21-acetate, m. p. 222—226°, $[\alpha]_D^{26}$ +78°, in 81% yield. Crystallisation from chloroform gave a specimen, m. p. 222—226°, $[\alpha]_D^{21}$ +81° (*c* 0·5), +80° (*c* 1·0 in dioxan), ν 1745, 1230, 1725, and 1700 cm.$^{-1}$ (Found: C, 68·1; H, 8·7. Calc. for $C_{23}H_{34}O_6$: C, 67·95; H, 8·4%). Pataki *et al.*[42] give m. p. 210—212°, $[\alpha]_D^{20}$ +69°, for this compound.

11β-*Acetoxy*-17α : 21-*dihydroxy*-5α-*pregnane*-3 : 20-*dione* (XII; R = O; R′ = H, β-OAc; R″ = H).—The 11β-acetoxy-bisketal (XIV; n = 2; R = H, β-OAc; R″ = H) (1 g.) was hydrolysed with methanolic sulphuric acid.[18] The *dione* named above was obtained from ether (as needles, 0·51 g., 62%) and then from acetone–hexane, m. p. 205—209°, $[\alpha]_D^{23}$ +60° (*c* 0·84), ν 1710, 1265, and 1700 cm.$^{-1}$ (Found: C, 68·1; H, 8·5. $C_{23}H_{34}O_6$ requires C, 67·95; H, 8·4%). The 11 : 21-*diacetate* formed solvated needles, m. p. 210—215° (after loss of solvent at 100—105°). The solvent-free compound, obtained at 100°/0·1 mm. in 2 hr., had m. p. 210—215°, $[\alpha]_D^{24}$ +85° (*c* 0·54), ν 1752 and 1225 (21-acetate), 1728 and 1245 (11β-acetate), and 1728 and 1692 cm.$^{-1}$ (Found: C, 66·8; H, 8·05. $C_{25}H_{36}O_7$ requires C, 66·9; H, 8·1%).

11β : 21-*Diacetoxy*-20 : 20-*ethylenedioxy*-17α-*hydroxy*-5α-*pregnan*-3-*one* (XV; R = H, β-OAc; R′ = Ac; X = Y = H).—This compound was made by selective hydrolysis of the bisketal (XIV; R = H, β-OAc; R′ = H) (0·63 g.) with acetone (20 ml.), water (3 ml.) and 2N-hydrochloric acid (0·25 ml.), as described before.[18] Isolation by means of methylene dichloride gave a gel which was acetylated by the usual method; the product was crystallised thrice from aqueous methanol and twice from hexane, giving needles of the 11 : 21-*diacetate* (XV; R = H, β-OAc; R′ = Ac; X = Y = H) (0·20 g., 32%), m. p. 164—166°, $[\alpha]_D^{23}$ +40° (*c* 0·6), ν (in CS_2) 1750 and 1240 (21-acetate), 1732 and 1240 (11β-acetate), 1716 and 1100 cm.$^{-1}$ (Found: C, 66·0; H, 8·4. $C_{27}H_{40}O_8$ requires C, 65·8; H, 8·2%).

21-*Acetoxy*-17α-*hydroxy*-5α-*pregn*-9-*ene*-3 : 20-*dione* (XVIII; R = Ac).—A solution of 4 : 5α-dihydrocortisol acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) (1 g.) in glacial acetic acid (40 ml.) was treated under nitrogen with 5·5N-hydrogen bromide in acetic acid (8 ml.). Crystals began to separate almost at once; after 20 min. the mixture was poured into sodium acetate solution and filtered, giving the Δ^9-*compound* (XVIII; R = Ac) (0·955 g.), m. p. 240—245° (capillary; decomp.). Recrystallisation from ethyl acetate gave plates (0·88 g., 92%), m. p. 244—253° (decomp.), $[\alpha]_D^{21}$ +62° (*c* 0·5), ν 1735, 1240, 1725, 1705, 1640, and 812 cm.$^{-1}$ (Found: C, 71·2; H, 8·2. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%). The same conversion took place within 0·5 hr. in solution in chloroform, but the yield of the Δ^9-compound was not so good (see below). The compound (XVIII; R = Ac) consumed 1 equiv. of permonophthalic acid within a few hr.

[42] Pataki, Rosenkranz, and Djerassi, *J. Biol. Chem.*, 1952, **195**, 751.

Action of Hydrogen Bromide on Solutions of 4 : 5α-*Dihydrocortisol Acetate* (XII; R = O; R′ = H, β-OH; R″ = Ac).—The change reported above pertains to chloroform solutions made 0·082N in hydrogen bromide; in 0·03N-solutions no change occurred. With 0·125N-hydrogen bromide in methylene dichloride as solvent the elimination was studied polarimetrically: such solutions, made 0·25M in methanol, ethanol, benzyl alcohol, ethyl acetate, or ether showed diminishing rotations in <15 min.; with alcohols this trend was reversed subsequently.[43] Addition of 10% (v/v) ether prolonged the duration of change to *ca.* 32 min. Diphenyl ether had no effect. In pure acetic acid made 0·37N in hydrogen bromide the elimination finished (with crystallisation) in <20 min. In 0·125N-hydrogen bromide in dioxan as sole solvent no change occurred during 3 hr., and the 11β-alcohol (XII; R = O; R′ = H, β-OH; R′ = Ac) was recovered almost quantitatively.

21-*Acetoxy*-2α-*bromo*-20 : 20-*ethylenedioxy*-17α-*hydroxy*-5α-*pregnane*-3 : 11-*dione* (XV; R = O; R′ = Ac; X = Br; Y = H).—A solution of the 20-ketal (XV; R = O; R′ = Ac; X = Y = H) (1 g.) in pure methylene chloride (15 ml.) was brominated in 0·5 min. with bromine (0·404 g., 1·15 mol.) in the same solvent (5 ml.). The isolated *bromo-ketone* (1·12 g.) crystallised from ethyl acetate as plates (0·87 g., 81%), m. p. 238—239° (decomp.), $[\alpha]_D^{23}$ +68° (*c* 1·0), ν (in $CHBr_3$) 1735, 1230, 1725, 1698, 1100, and 819 cm.$^{-1}$ (Found: C, 56·8; H, 6·5; Br, 15·3. $C_{25}H_{35}O_7Br$ requires C, 56·9; H, 6·7; Br, 15·15%).

21-*Acetoxy*-4α-*bromo*-20 : 20-*ethylenedioxy*-17α-*hydroxy*-5α-*pregnane*-3 : 11-*dione* (XV; R = O; R′ = Ac; X = H; Y = Br).—The crude 2 : 4-dibromo-compound (XV; R = O; R′ = Ac; X = Y = Br) was made by treating the ketal (XV; R = O; R′ = Ac; X = Y = H) (5 g.) in pure methylene dichloride (75 ml.) and ether (15 ml.) at 20° with bromine (4·04 g., 2·3 mol.) in methylene chloride (45 ml.) during 17 min. (a drop of hydrogen bromide in methylene chloride was used to initiate the halogenation). The solution was then neutralised and the steroid extracted and washed (7·7 g.). This dibromo-substance (which could not be purified) was partially dehalogenated [1] in acetic acid (150 ml.), chloroform (40 ml.), and methylene dichloride (25 ml.) at −5° under carbon dioxide with 1·15N-chromous chloride (22·8 ml., 1·2 equiv.), with stirring during 15 min. The solution was kept for another 15 min., then poured into water. The extracted steroid (5·85 g.), m. p. 190—208°, $[\alpha]_D^{22}$ +35° (Found: Br, 16·2%), was fractionally crystallised from ethyl acetate, then from chloroform, giving the 4-bromo-ketal (XV; R = O; R′ = Ac; X = H; Y = Br) (0·61 g., 12%), m. p. 240—241°, $[\alpha]_D^{22}$ +24°. Other crops contained 1·73 g. (32%), m. p. >236°, $[\alpha]_D$ <+30°. (All these fractions melted with decomp.)

A specimen, recrystallised from ethyl acetate, had m. p. 240—244° (decomp.), $[\alpha]_D^{22}$ +24° (*c* 0·55), ν 1744, 1226, 1726, and 1696 cm.$^{-1}$ (Found: C, 57·1; H, 6·65; Br, 15·15. $C_{25}H_{35}O_7Br$ requires C, 56·9; H, 6·7; Br, 15·15%).

The foregoing 4-bromo-ketal (100 mg.) was converted into 21-acetoxy-20 : 20-ethylenedioxy-17α-hydroxypregn-4-ene-3 : 11-dione (XVI; R = O; R′ = Ac) (50 mg., 59%), m. p. 203—206°, *via* the semicarbazone of the latter, by the method given in a preceding paper.[1] Crystallisation from acetone–ether gave the pure product, m. p. 204—209°, $[\alpha]_D^{24}$ +152° (*c* 0·9), $\lambda_{max.}$ 237·5 mμ (ε 15,300), ν 1742, 1230, 1696, 1665, and 1616 cm.$^{-1}$ {lit.,[18] m. p. 212—215°, $[\alpha]_D^{20}$ +153°, $\lambda_{max.}$ 237—238 (ε 16,700)}.

20 : 20-*Ethylenedioxy*-11β : 17α : 21-*trihydroxypregn*-4-*en*-3-*one* (XVI; R = H, β-OH; R′ = H).—The 4-bromo-ketal (XV; R = O; R′ = Ac; X = H; Y = Br) (1·2 g.) was converted into its 3-semicarbazone; [1] without purification this was reduced in 1 hr. in refluxing ethanol (25 ml.) and water (5 ml.) containing potassium hydrogen carbonate (0·45 g.) and sodium borohydride (0·6 g.). The steroid was isolated from the neutralised product and dissolved in acetic acid (7 ml.), water (2·5 ml.) and " 50—60% " pyruvic acid (2 ml.). The solution was kept for 17·5 hr. The extracted steroid (0·28 g.) crystallised from acetone as needles (45 mg., 5%) of the *trihydroxy-ketal* (XVI; R = H, β-OH; R′ = H), m. p. 219—221°, $[\alpha]_D^{26}$ +109° (*c* 0·5), $\lambda_{max.}$ 241·5 mμ (ε 15,400), ν 1670, 1618, 865, and 1105 cm.$^{-1}$ (Found: C, 67·5; H, 8·4. $C_{23}H_{34}O_6$ requires C, 68·0; H, 8·4%).

2-*Bromo*-4 : 5α-*dihydrocortisol Acetate* (XIX).—Dihydrocortisol acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) (20 g.) was dissolved in warm dioxan (200 ml.) and cooled to 23°. Bromine (2·8 ml.) was added in 20 sec., and after 1½ min. the pale yellow solution was poured into aqueous sodium hydrogen carbonate. The dry precipitate gave crystals (14·9 g., 62%), m. p. 182° (decomp.), from aqueous acetic acid. Further crystallisation from this solvent and

[43] Cf. Mattox, *J. Amer. Chem. Soc.*, 1952, **74**, 4340; Taub, Pettebone, Wendler, and Tishler, *ibid.*, 1954, **76**, 4094; Mancera, Rosenkranz, and Sondheimer, *ibid.*, 1955, **77**, 5669.

from ethyl acetate–hexane gave the pure 2-*bromo-ketone* (XIX), m. p. 185—186° (decomp.), $[\alpha]_D^{20}$ +97° (*c* 0·7), ν 1714 and 1250 cm.$^{-1}$ (Found: C, 56·4; H, 6·8; Br, 16·0. $C_{23}H_{33}O_6Br$ requires C, 56·9; H, 6·8; Br, 16·4%).

Debromination with zinc and acetic acid of the mother-liquors [1] and crystallisation of the product yielded 4 : 5α-dihydrocortisol acetate (3·42 g.). Debromination likewise of the pure bromo-compound (XIX) gave pure dihydrocortisol acetate in 72% yield.

2 : 2-*Dibromo*-4 : 5α-*dihydrocortisol Acetate* (XX).—A solution of the 2-bromo-compound (XIX) (2 g.) in dioxan (86 ml.) was treated with bromine (0·24 ml.) and 6N-hydrogen bromide in acetic acid (2 drops). The rotation reached a maximum in 15 min., and the solution was then poured into aqueous sodium hydrogen carbonate. The dried precipitate (2·18 g.), m. p. 125° (decomp.), $[\alpha]_D$ +111° (Found: Br, 26·6%), crystallised with difficulty from ethyl acetate–hexane and methylene dichloride, to give the 2 : 2-*dibromo-ketone* (XX), m. p. 155° (decomp.), $[\alpha]_D^{20}$ +161° (*c* 0·53), ν (in $CHBr_3$) 1742, 1240, and 1726 cm.$^{-1}$ (Found: C, 48·2; H, 5·7; Br, 28·7. $C_{23}H_{32}O_6Br_2$ requires C, 49·0; H, 5·7; Br, 28·3%). Crystallisation from benzene yielded a *solvate*, m. p. 139—142° (decomp.), $[\alpha]_D^{20}$ +134° (*c* 1·0), with the foregoing bands in the infrared spectrum and an additional peak at 1485 cm.$^{-1}$ (benzene) (Found: Br, 24·0. $C_{23}H_{32}O_6Br_2,C_6H_6$ requires Br, 25·0%). Debromination with zinc and acetic acid gave pure 4 : 5α-dihydrocortisol acetate in 89% yield.

Bromination of the ketone (XIX) in methylene dichloride and *tert.*-butyl alcohol (3 : 1) for 3 hr. yielded 2-bromo-4 : 5α-dihydrocortisone acetate, debromination of which gave 4 : 5α-dihydrocortisone acetate.[1] Attempts at base-catalysed bromination [1] gave similar results.

Cortisol Acetate (XIII; R = H, β-OH; R′ = Ac).—4 : 5α-Dihydrocortisol acetate (XII; R = O; R′ = H, β-OH; R″ = Ac) (1 g.) in dioxan (43 ml.) was treated with 4N-hydrogen bromide in dioxan (1 drop) and bromine (0·863 g.) in 45 sec. The pale yellow solution was kept at 20° for 50 min. and neutralised with sodium hydrogen carbonate in much water. The precipitated dibromo-compound (1·145 g.), $[\alpha]_D^{18}$ +47° (Found: Br, 28·5%), was treated with sodium iodide (3·6 g.) in acetone (60 ml.) containing bromoacetone, as described previously.[1] Segregation of the αβ-unsaturated ketone in the product by means of its Girard derivative and crystallisation from ethyl acetate, then from acetone, gave rhombs (0·10 g., 10%) of cortisol acetate, m. p. 215—221°, $[\alpha]_D^{24}$ +158° (*c* 0·6 in dioxan), $\lambda_{max.}$ 242 mμ (ε 15,200), ν (in $CHCl_3$) 1745, 1726, 1664, and 1618 cm.$^{-1}$ (Found: C, 68·5; H, 7·95. Calc. for $C_{23}H_{32}O_6$: C, 68·3; H, 8·0%) {lit.,[44] m. p. 218—221·5°, $[\alpha]_D^{25}$ +158° (in dioxan), $\lambda_{max.}$ (in MeOH) 242 mμ (ε 15,350)}.

21-*Acetoxy*-17α-*hydroxypregna*-4 : 9-*diene*-3 : 20-*dione* (XVII).—The Δ^9-steroid (XVIII; R = Ac) (1·2 g.) in suspension in anhydrous methylene dichloride (27 ml.) and ether (6 ml.) was treated with bromine (0·349 ml., 2·2 mol.) in methylene chloride (2 ml.). The first mol. of halogen was consumed within 4 min., during which most of the steroid dissolved and was reprecipitated. Consumption of the second mol. took another 7·5 min., and resulted in a pale yellow solution, which was kept for another 6 min. before being washed with sodium hydrogen carbonate and water. The extracted steroid was treated with sodium iodide (2·5 g.) and acetone (25 ml.) containing bromoacetone, as previously described.[1] Subsequent dehalogenation and purification of the product (1·2 g.) by means of Girard derivatives afforded material (0·5 g.) of low ultraviolet absorption, probably being mainly the starting material (XVIII; R = Ac) (see below). The more stable Girard reagent yielded material (0·54 g.) crystallising from acetone (charcoal) as flat rods (0·37 g.) of the solvated *diene-dione* (XVII), m. p. 231—234° (slight decomp.), with loss of solvent at 110—120°. Drying at 140°/0·1 mm. furnished the solvent-free compound (0·315 g., 26%), $[\alpha]_D^{21}$ +124° (*c* 0·87), $\lambda_{max.}$ 239 mμ (ε 16,400), ν 1745, 1240, 1723, 1655, and 1618 cm.$^{-1}$. Graber *et al.*[2] give m. p. 231·5—234·5°, $[\alpha]_D^{23}$ +124°, $\lambda_{max.}$ (in MeOH) 240 mμ (ε 15,800), and Bernstein *et al.*[45] m. p. 239·5—241°, $\lambda_{max.}$ 238·5—240 mμ (ε 16,600), ν 1775, 1730, 1660, and 1620 cm.$^{-1}$

During the isolation of the Girard derivatives above, insoluble material, $\lambda_{max.}$ 267 mμ ($E_{1\,cm.}^{1\%}$ 228), was precipitated. Treatment with acid generated the 4 : 5-dihydro-compound (XVIII; R = Ac), which was combined with material got from the Girard derivative that had stayed in solution. It seemed possible that the use of the Girard derivatives was unnecessary, the separation being achieved by crystallisation.

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[*Received, November* 21*st*, 1957.]

[44] Wendler, Graber, Jones, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 3630.
[45] Bernstein, Littell, and Williams, *ibid.*, 1953, **75**, 4830.

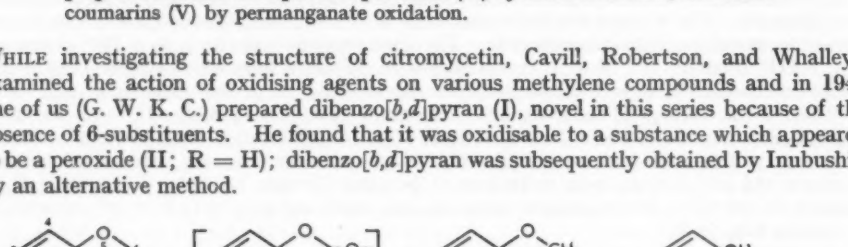
XUM

307. *Dibenzo*[b,d]*pyrans and Related Products.*

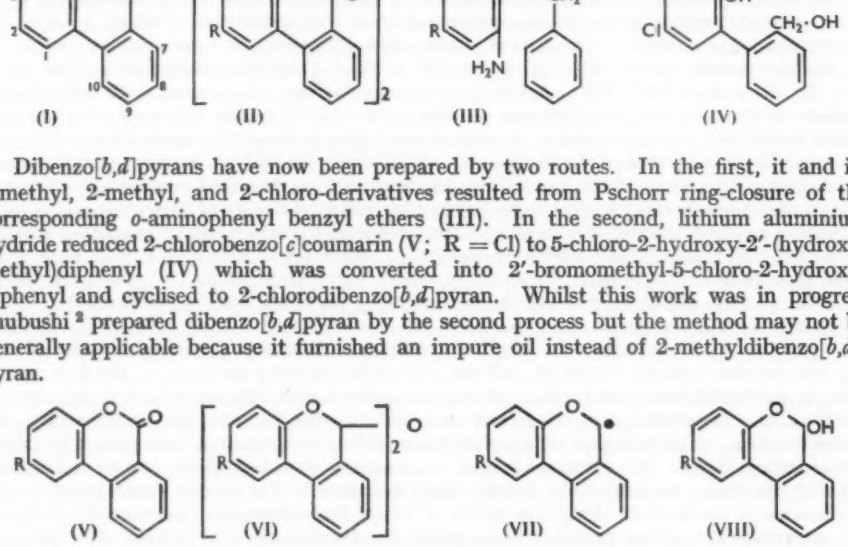
By G. W. K. Cavill, F. M. Dean, J. F. E. Keenan, A. McGookin, Alexander Robertson, and G. B. Smith.

Dibenzo[*b*,*d*]pyrans (cf. I) not substituted in the 6-position have been prepared and shown to produce peroxides (II) by aerial oxidation, and benzocoumarins (V) by permanganate oxidation.

While investigating the structure of citromycetin, Cavill, Robertson, and Whalley [1] examined the action of oxidising agents on various methylene compounds and in 1949 one of us (G. W. K. C.) prepared dibenzo[*b*,*d*]pyran (I), novel in this series because of the absence of 6-substituents. He found that it was oxidisable to a substance which appeared to be a peroxide (II; R = H); dibenzo[*b*,*d*]pyran was subsequently obtained by Inubushi [2] by an alternative method.



Dibenzo[*b*,*d*]pyrans have now been prepared by two routes. In the first, it and its 9-methyl, 2-methyl, and 2-chloro-derivatives resulted from Pschorr ring-closure of the corresponding *o*-aminophenyl benzyl ethers (III). In the second, lithium aluminium hydride reduced 2-chlorobenzo[*c*]coumarin (V; R = Cl) to 5-chloro-2-hydroxy-2′-(hydroxymethyl)diphenyl (IV) which was converted into 2′-bromomethyl-5-chloro-2-hydroxydiphenyl and cyclised to 2-chlorodibenzo[*b*,*d*]pyran. Whilst this work was in progress Inubushi [2] prepared dibenzo[*b*,*d*]pyran by the second process but the method may not be generally applicable because it furnished an impure oil instead of 2-methyldibenzo[*b*,*d*]-pyran.



Except for the 2-chloro-derivative, the dibenzopyrans prepared were oils and difficult to purify. For this reason the 2 : 3-dimethoxy- and 3-methoxy-derivatives were not analysed but were oxidised by chromic oxide or potassium permanganate in acetone to the solid benzocoumarins, a method well suited to the characterisation of such dibenzopyrans. For comparison, authentic benzo[*c*]coumarins (dibenzo-2-pyrones) of type (V) were generally prepared by a modification of Cahn's method [3] using anthranilic acid diazonium sulphate and phenols substituted in the *para*-position to avoid the formation of isomerides: the exception was 2 : 3-dimethoxybenzo[*c*]coumarin which was obtained by dehydrogenation of the corresponding *cyclo*hexenocoumarin (cf. Ghosh, Todd, and Wilkinson [4]).

Although small quantities of benzocoumarins (V) are formed by aerial oxidation of the

[1] Cavill, Robertson, and Whalley, *J.*, 1949, 1567.
[2] Inubushi, *J. Pharm. Soc. Japan*, 1952, **72**, 656; *Chem. Abs.*, 1953, **47**, 2173.
[3] Cahn, *J.*, 1933, 1400.
[4] Ghosh, Todd, and Wilkinson, *J.*, 1940, 1393.

dibenzopyrans, the main products are the corresponding peroxides (II). These compounds are probably produced through free radicals (VII) because this slow oxidation is considerably accelerated by the addition of benzaldehyde which is known to promote similar radical reactions [5] and because dixanthylethanes are known to dissociate into analogous radicals which then react with oxygen giving dixanthyl peroxides.[6]

Our peroxides were stable solids with fairly high melting points, inert to potassium iodide, and resisted hydrogenation. However, reduction with zinc and acetic anhydride was partially successful and gave the chloro- (VI; R = Cl) and the methyl-substituted ether (VI; R = Me) from the corresponding peroxides (II); concentrated sulphuric acid has a similar effect. The view that the intermediate in these reactions is the alcohol (VIII) which, by dehydration of two molecules affords the ether, or by aerial oxidation of one molecule gives the benzocoumarin, is not only supported by the formation of xanthones in the autoxidation of dixanthylethanes and the formation of xanthhydrols when sulphuric acid reacts with dixanthyl peroxides,[6] but also neatly accommodates the formation of 2-chlorobenzo[*c*]coumarin (V; R = Cl) as the sole "reduction" product when lithium aluminium hydride interacts with the peroxide (II; R = Cl). The same chlorocoumarin (V; R = Cl) is obtained by the action of pyridine and acetic anhydride on the peroxide (II; R = Cl) and may then result from decomposition of an acetyl dibenzopyranyl peroxide.

The infrared absorption spectra of the chloro-peroxide (II; R = Cl) and chloro-ether (VI; R = Cl), and of the methyl peroxide (II; R = Me) and methyl ether (VI; R = Me) are almost identical and do not contain peaks that must be attributed to hydroxyl or carbonyl groups. A striking feature of the ethers is the very broad and strong band at 947 cm.$^{-1}$ which is resolved in the spectra of the peroxides into two strong bands at 963 and 945 cm.$^{-1}$. Since the stretching vibration of the peroxide link is weak and not characteristic,[7] it is reasonable to associate these bands (which are absent from spectra of the dibenzopyrans and benzocoumarins) with the acetal groupings of the systems (II) and (VI). The frequencies are somewhat lower than those usually associated with ethers or with the CH vibrations of acetals,[8] but since interactions can be expected in symmetrical systems the data are accepted as supporting evidence for the structures assigned to the peroxides (II) and the ethers (VI).

2-Chloro-6 : 6-diphenyldibenzo[*b*,*d*]pyran was obtained from 2-chlorobenzo[*c*]coumarin by means of phenylmagnesium bromide in excess and, as expected, was stable in air. With a limited quantity of the Grignard reagent, this coumarin supplied an alcohol which could not be isolated but was converted into crystalline 2-chloro-6-phenyldibenzo[*b*,*d*]-pyran-6-yl perchlorate. Attempts to prepare similar salts by reduction of our peroxides in acid media failed.

Experimental

Dibenzo[b,d]*pyran.*—Suspended in 2N-sulphuric acid (400 ml.) at 0°, *o*-aminophenyl benzyl ether hydrochloride (20 g.) was diazotised with a solution of sodium nitrite (6 g.) in water (25 ml.), added during ½ hr. The mixture was then kept for ½ hr., filtered to remove a trace of solid, and, after the addition of copper bronze (4 g.), was rapidly stirred for 4 hr. The product tended to form a sludge with the copper bronze, more of which was added at intervals to ensure complete reaction. Next day the filtered solution was extracted with ether, and the extract washed with water, dried, and evaporated, leaving a brown oil which was chromatographed from light petroleum (b. p. 40—60°) on aluminium oxide. On elution the resulting colourless oil (7·5 g.) was distilled, giving dibenzo[*b*,*d*]pyran, b. p. 138—141°/2·5 mm. (Found: C, 85·1; H, 5·8. Calc. for $C_{13}H_{10}O$: C, 85·7; H, 5·5%).

[5] Waters, "The Chemistry of Free Radicals," 2nd edn., Oxford Univ. Press.
[6] Conant and Sloan, *J. Amer. Chem. Soc.*, 1925, **47**, 572 and later papers.
[7] Davison, *J.*, 1951, 2456.
[8] Bergman and Pinchas, *Rec. trav. chim.*, 1952, **71**, 161.

A solution of the dibenzopyran (1 g.) in glacial acetic acid (20 ml.) was warmed on a steam-bath for 1 hr. with chromic oxide (1 g.). The ethereal extract of the mixture was washed with dilute alkali and then water, dried, and evaporated, leaving benzo[*c*]coumarin (dibenzo-2-pyrone) [9] which crystallised from benzene–light petroleum (b. p. 60—80°) in prisms (0·4 g.), m. p. 95°. Oxidation of the dibenzopyran (1 g.) with potassium permanganate (1·5 g.) in boiling acetone (100 ml.) gave the same coumarin (0·6 g.), m. p. and mixed m. p. 95°.

2-Chlorodibenzo[b,d]*pyran.*—(*a*) 2-Amino-4-chlorophenyl benzyl ether hydrochloride (20 g.) was diazotised and converted into *2-chlorodibenzo*[b,d]*pyran* by the foregoing procedure. This compound separated from methanol in prisms (8 g.), m. p. 47° (Found: C, 71·6; H, 4·2. $C_{13}H_9OCl$ requires C, 72·1; H, 4·2%). Oxidised by the methods given above, this compound gave *2-chlorobenzo*[c]*coumarin*, separating from acetic acid in needles, m. p. 181° (Found: C, 67·5; H, 3·2; Cl, 15·4. $C_{13}H_7O_2Cl$ requires C, 67·7; H, 3·0; Cl, 15·4%). An authentic specimen of this coumarin was prepared by gently warming an intimate mixture of anthranilic acid diazonium sulphate (40 g.) and *p*-chlorophenol (40 g.) in a rotating flask. When the initial vigorous reaction had subsided somewhat, *p*-chlorophenol (40 g.) was added and heating was intensified until nitrogen was no longer evolved, whereupon removal of acidic materials by means of aqueous sodium hydroxide left the chlorocoumarin which, on purification from acetic acid, formed needles (10·5 g.), m. p. and mixed m. p. 181°.

(*b*) Suspended in dry ether (1500 ml.), 2-chlorobenzo[*c*]coumarin (6 g.) was added slowly to a well-stirred solution of lithium aluminium hydride (2 g.) in the minimum amount of ether. 1 Hr. later wet ether and then dilute sulphuric acid were added. The organic layer was freed from acid, dried, and evaporated, giving *5-chloro-2-hydroxy-2′-(hydroxymethyl)diphenyl* which separated from benzene–light petroleum (b. p. 80—100°) in needles (5·7 g.), m. p. 104—106° (Found: C, 66·5; H, 4·9; Cl, 15·1. $C_{13}H_{11}O_2Cl$ requires C, 66·6; H, 4·7; Cl, 15·1%). The *di-p-nitrobenzoate* had m. p. 122—123° (Found: C, 60·9; H, 2·9; N, 5·1. $C_{27}H_{17}O_8N_2Cl$ requires C, 60·9; H, 3·2; N, 5·3%).

A solution of this diol (5 g.) in dry benzene (120 ml.) was saturated with anhydrous hydrogen bromide, washed free from acid, dried (Na_2SO_4), and evaporated, leaving the *bromide* (4·75 g.) which was purified from light petroleum (b. p. 40—60°), m. p. 85—87° (Found: C, 52·4; H, 3·3. $C_{13}H_{10}OBrCl$ requires C, 52·4; H, 3·4%), and formed a *phenylurethane*, m. p. 150° (Found: C, 57·8; H, 3·5. $C_{20}H_{15}O_2NBrCl$ requires C, 57·7; H, 3·6%). When this bromide (3·0 g.) in the minimum of methanol was treated with N-methanolic potassium hydroxide (3 ml.), the solution rapidly became warm and deposited potassium chloride. Isolated by means of ether and freed from phenols by aqueous potassium hydroxide, the product was washed with water, dried *in vacuo*, and crystallised from light petroleum (b. p. 40—60°), giving *2-chlorodibenzo*-[b,d]*pyran* in prisms, m. p. and mixed m. p. 47° (Found: C, 72·2; H, 4·5; Cl, 16·3. $C_{13}H_9OCl$ requires C, 72·1; H, 4·2; Cl, 16·4%).

9-Methyldibenzo[b,d]*pyran.*—A mixture of *o*-nitrophenol (30 g.), *p*-xylyl chloride (27 g.), potassium iodide (10 g.), and anhydrous potassium carbonate (60 g.) was heated in acetone (200 ml.) for 12 hr. When the oily product was triturated with light petroleum (b. p. 60—80°) it solidified and the resulting *o-nitrophenyl p-xylyl ether* crystallised from chloroform–light petroleum (b. p. 60—80°), forming pale yellow needles (22 g.), m. p. 68° (Found: C, 68·8; H, 5·5; N, 5·5. $C_{14}H_{13}O_3N$ requires C, 69·1; H, 5·4; N, 5·8%). *o-Aminophenyl p-xylyl ether* resulted in 71% yield from reduction of the nitro-compound with sodium polysulphide and formed needles, m. p. 82°, when purified from light petroleum (b. p. 60—80°) (Found: C, 78·3; H, 6·8; N, 6·6. $C_{14}H_{15}ON$ requires C, 78·8; H, 7·1; N, 6·6%). With gaseous hydrogen chloride this amine in ether gave the hydrochloride (10 g.), the diazonium salt from which decomposed to a pale yellow oil that distilled at 98—101°/0·01 mm., giving *9-methyldibenzo*[b,d]*pyran* (2·4 g.) (Found: C, 85·4; H, 6·4. $C_{14}H_{12}O$ requires C, 85·7; H, 6·2%). The oxidation of this with permanganate or chromic acid furnished *9-methylbenzo*[b]*coumarin* which crystallised from alcohol in prisms (55% yield), m. p. 164° (Found: C, 79·5; H, 4·9. $C_{14}H_{10}O_2$ requires C, 80·0; H, 4·8%).

2-Methyldibenzo[b,d]*pyran.*—A mixture of *o*-nitrobenzyl *p*-tolyl ether [10] (22 g.) in alcohol (300 ml.), sodium sulphide (48 g.), and sulphur (8 g.) was heated under reflux for 6—7 hr. and after the usual purification an ethereal solution of the amine was saturated with hydrogen chloride and the precipitated salt crystallised from glacial acetic acid, furnishing *o-aminobenzyl*

[9] Rule and Bretscher, *J.*, 1927, 925.
[10] Frische, *Annalen*, 1884, **224**, 142.

p-*tolyl ether hydrochloride* in plates (19 g.), m. p. 202° (Found: C, 67·0; H, 6·3. $C_{14}H_{16}ONCl$ requires C, 67·3; H, 6·4%). This hydrochloride (15 g.) was diazotised and treated with copper bronze, giving 2-*methyldibenzo*[b,d]*pyran* (5 g.), b. p. 122—124°/1 mm. (Found: C, 85·4; H, 6·2. $C_{14}H_{12}O$ requires C, 85·7; H, 6·2%). Oxidation of this with permanganate or chromic acid gave 2-*methylbenzo*[c]*coumarin* which formed needles, m. p. 133°, from methanol (Found: C, 80·0; H, 5·0. $C_{14}H_{10}O_2$ requires C, 80·0; H, 4·8%). The same coumarin resulted from the addition of small portions of anthranilic acid diazonium sulphate (18 g.) to *p*-cresol in a gently warmed and constantly rotating flask and, when isolated from the cooled mixture by means of ether and freed from phenols by means of aqueous sodium hydroxide, separated from methanol in needles (17·1 g.), m. p. and mixed m. p. 134°.

2-*Chloro*-6 : 6-*diphenyldibenzo*[b,d]*pyran*.—To phenylmagnesium bromide (from 4·5 g. of bromobenzene) was added 2-chlorobenzo[*c*]coumarin (1·0 g.) in benzene (50 ml.). After filtration and evaporation of the solvent the mixture gave 2-*chloro*-6 : 6-*diphenyldibenzo*[b,d]-*pyran* which on purification from alcohol formed prisms (1·1 g.), m. p. 197°, insoluble in alkali (Found: C, 81·3; H, 4·8; Cl, 9·6. $C_{25}H_{17}OCl$ requires C, 81·4; H, 4·6; Cl, 9·6%).

Bis(*dibenzo*[b,d]*pyran*-6-*yl*) *Peroxide*.—Dibenzo[*b,d*]pyran (1 g.) in chloroform (50 ml.) was ozonised for ½ hr. Removal of the solvent left a brown oil which crystallised from acetic acid, affording the *peroxide* (0·08 g.), m. p. 186° (Found: C, 78·8; H, 4·8. $C_{26}H_{18}O_4$ requires C, 79·2; H, 4·6%). The same product was obtained when the dibenzopyran (1 g.) in glacial acetic acid was exposed to the air; the peroxide, m. p. 186°, separated during 6 days.

Di-(2-*chlorodibenzo*[b,d]*pyran*-6-*yl*) *Peroxide*.—2-Chlorodibenzo[*b,d*]pyran (1·5 g.) in glacial acetic acid (70 ml.) was kept in air for 8 days. The precipitate which slowly separated was crystallised from ethyl acetate, giving the *peroxide* (1·05 g.) in needles, m. p. 196° (decomp.) (Found: C, 67·2; H, 3·7; Cl, 15·3. $C_{26}H_{16}O_4Cl_2$ requires C, 67·4; H, 3·5; Cl, 15·3%). The residual acetic acid solution was diluted with water and the solid product isolated with ether, washed with aqueous sodium hydroxide, and crystallised from methanol, giving 2-chlorodibenzo[*c*]coumarin (0·15 g.), m. p. and mixed m. p. 181°. The addition of benzaldehyde (3 ml.) during the oxidation almost doubled its rate, but the addition of *tert.*-butyl hydroperoxide or cobalt naphthenate had but little effect.

Oxidation of the dibenzopyran with hydrogen peroxide in acetic acid gave an 18% yield of 2-chlorobenzo[*c*]coumarin, the remaining material being resinous. On being kept in nitrogen for 28 days 2-chlorodibenzo[*b,d*]pyran, dissolved in glacial acetic acid, was recovered unchanged but when it (0·5 g.) was heated with benzaldehyde in acetic acid (30 ml.) at 120° for 50 hr. an orange solution was formed which contained a neutral water-insoluble material and was purified by chromatography on aluminium oxide from benzene, giving 2-chlorobenzo[*c*]coumarin (0·3 g.), m. p. and mixed m. p. 181°. The same coumarin, m. p. and mixed m. p. 181°, resulted when: (*a*) the peroxide (0·5 g.) in diethylene glycol diethyl ether was added to lithium aluminium hydride (0·1 g.) in the same solvent (25 ml.) and kept at 120° for 6 hr.; careful dilution with water, followed by dissolution of the metallic hydroxides in dilute sulphuric acid, left a crystalline residue of the coumarin (0·18 g.); and (*b*) the peroxide (0·1 g.) and pyridine (25 ml.) were heated for 5 min. under reflux in an excess of acetic anhydride and the product was isolated in the conventional fashion and purified from benzene on a column of aluminium oxide.

Di-(2-*chlorodibenzo*[b,d]*pyran*-6-*yl*) *Ether*.—(*a*) A solution of the peroxide (0·5 g.) in boiling acetic acid (80 ml.) was gradually treated during 4 hr. with zinc dust (0·5 g.) and a large excess of acetic anhydride. An ethereal solution of the product was washed, dried, and evaporated and the residue triturated with benzene–light petroleum (b. p. 60—80°) and then purified from ethyl acetate, giving *di*-(2-*chlorodibenzo*[b,d]*pyran*-6-*yl*) *ether* in plates (0·05 g.), m. p. 231°. (*b*) The green solution of the peroxide (0·5 g.) in sulphuric acid (20 ml.) rapidly became brown and when poured on ice gave a precipitate which, in ether, was freed from acid. The product was dried by distillation of a solution in benzene and, after desiccation *in vacuo*, was chromatographed from benzene on a column of aluminium oxide. Thus obtained di-(2-chlorodibenzo-[*b,d*]pyran-6-yl) ether (0·2 g.), m. p. 232°, was identical with a specimen prepared as in (*a*) (Found: C, 70·0; H, 3·9; Cl, 16·1. $C_{26}H_{16}O_3Cl_2$ requires C, 69·8; H, 3·6; Cl, 15·9%).

Di-(2-*methyldibenzo*[b,d]*pyran*-6-*yl*) *Peroxide*.—(*a*) Ozonised in chloroform (20 ml.) for ½ hr., 2-methyldibenzo[*b,d*]pyran (1 g.) furnished the *peroxide* in prisms (0·05 g.), m. p. 185° (decomp.), from benzene. The m. p. of this was depressed on admixture with bis(dibenzo[*b,d*]pyran-6-yl) peroxide, m. p. 186°. (*b*) Exposed to air for 5 days 2-methyldibenzo[*b,d*]pyran (1·25 g.) in acetic acid (100 ml.) afforded the peroxide (0·87 g.), m. p. 185° (Found: C, 79·4; H,

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5·2. $C_{33}H_{22}O_4$ requires C, 79·6; H, 5·3%), accompanied by 2-methylbenzo[*c*]coumarin (0·07 g.), m. p. 134—135°.

Di-(2-methyldibenzo[b,d]*pyran-6-yl) Ether.*—As in the previous example, the peroxide (0·5 g.) with sulphuric acid (20 ml.) afforded the *ether* (0·17 g.), m. p. 200°, after purification from ethyl acetate (Found: C, 83·1; H, 5·6. $C_{26}H_{22}O_3$ requires C, 82·7; H, 5·5%).

4-Methoxy-2-methylbenzo[b]*coumarin* was obtained by a modification of Cahn's method, with use of creosol, and separated from alcohol in needles (yield 23%), m. p. 207—208° (Found: C, 74·9; H, 5·3; OMe, 12·8. $C_{18}H_{12}O_3$ requires C, 75·0; H, 5·0; OMe, 12·9%).

8-Bromo-2-methylbenzo[c]*coumarin* was formed by the interaction of 5-bromoanthranilic acid diazonium sulphate (31 g.) with *p*-cresol and formed needles (10·4 g.), m. p. 172°, from alcohol (Found: C, 58·2; H, 2·9; Br, 27·7. $C_{14}H_9O_2Br$ requires C, 58·1; H, 3·1; Br, 27·7%).

8 : 10-Dibromo-2-methylbenzo[c]*coumarin* was obtained by decomposition of 3 : 5-dibromoanthranilic acid diazonium sulphate (27·6 g.) in *p*-cresol (12 g.) and separated from alcohol in needles (5·5 g.), m. p. 184° (Found: Br, 42·1. $C_{14}H_8O_2Br_2$ requires Br, 43·4%. Because of its somewhat unusual elementary composition, this compound did not give satisfactory analytical values for C and H).

7 : 8 : 9 : 10-Tetrahydro-2 : 3-dimethoxybenzo[c]*coumarin.*—Condensation of 4-hydroxyveratrole (1 g.) and ethyl 2-oxo*cyclo*hexanecarboxylate (1·1 g.) was induced by gradual addition of concentrated sulphuric acid (2 ml.) in the cold (cf. Ghosh, Todd, and Wilkinson [4]). After 24 hr. the mixture was poured on ice, and the solid product crystallised from alcohol, giving the *product* (0·6 g.) in needles, m. p. 182° (Found: C, 68·8; H, 6·2; OMe, 23·8. $C_{15}H_{16}O_4$ requires C, 69·2; H, 6·2; OMe, 23·8%).

2 : 3-Dimethoxybenzo[c]*coumarin.*—(*a*) The diazonium salt from 2-aminobenzyl 3 : 4-dimethoxyphenyl ether (4·7 g.) was decomposed, giving the oily 2 : 3-dimethoxydibenzo[*b,d*]pyran which was directly oxidised with potassium permanganate to the coumarin, m. p. 177°. (*b*) When 7 : 8 : 9 : 10-tetrahydro-2 : 3-dimethoxybenzo[*c*]coumarin (0·2 g.) was dehydrogenated with palladium–charcoal in nitrogen at 320°, the benzocoumarin sublimed on to a cold finger and then formed needles (0·1 g.), m. p. 177°, from methanol (Found: C, 70·0; H, 4·6; OMe, 24·2. $C_{15}H_{12}O_4$ requires C, 70·3; H, 4·7; OMe, 24·2%).

2-Methoxybenzo[c]*coumarin* was prepared by Cahn's method and separated from methanol, m. p. 166—168° (Found: C, 74·2; H, 4·5; OMe, 13·7. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·5; OMe, 13·7%), in 13·5% yield.

3-Methoxybenzo[c]*coumarin.*—4-Nitroresorcinol 1-methyl ether (20 g.) was etherified with benzyl bromide (8 ml.) and potassium carbonate in boiling acetone, giving *benzyl 5-methoxy-2-nitrophenyl ether* as yellowish needles (21 g.), m. p. 73°, from light petroleum (b. p. 60—80°) (Found: C, 64·8; H, 5·1; N, 5·4. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·1; N, 5·4%). Reduced with sodium polysulphide this ether gave 2-amino-5-methoxyphenyl benzyl ether isolated as the *hydrochloride* (3·3 g.), m. p. 220° (Found: C, 62·8; H, 5·8; N, 5·2. $C_{14}H_{16}O_2NCl$ requires C, 63·3; H, 6·0; N, 5·3%). On diazotisation, this hydrochloride (3 g.) afforded 3-methoxydibenzo[*b,d*]pyran as an oil which was directly oxidised by potassium permanganate to 3-methoxybenzo[*c*]coumarin (1·4 g.), m. p. and mixed m. p. 143° (cf. Hurtley [11]).

*8-iso*Propylbenzo[c]*coumarin* was prepared by the decomposition of anthranilic acid diazonium sulphate (18 g.) in *p-iso*propylphenol (40 g.) and formed needles (5·4 g.), m. p. 128—129°, from methanol (Found: C, 80·5; H, 6·1. $C_{16}H_{14}O_2$ requires C, 80·6; H, 5·9%).

2-Chloro-6-phenyldibenzo[b,d]*pyran-6-yl Perchlorate.*—To a stirred ethereal solution of phenylmagnesium bromide from bromobenzene (1·55 g.), 2-chlorobenzo[*c*]coumarin (1·0 g.) in dry ether was added slowly and ½ hr. later the mixture was poured on ice and dilute hydrochloric acid. The orange layer was washed free from acid and dried, the solvent was distilled, and the solution of the oily residue in anhydrous ether was saturated with hydrogen chloride, whereupon an orange precipitate was formed at 0° but redissolved at room temperature. Addition of 60% perchloric acid gave the *perchlorate* (1·1 g.) which on purification from glacial acetic acid had m. p. 250° (Found: Cl, 18·2. $C_{19}H_{12}O_6Cl_2$ requires C, 18·2%). This perchlorate exploded above its m. p.

3 : 4-Dimethoxyphenyl 2-nitrobenzyl ether was prepared from 4-hydroxyveratrole (10 g.) with 2-nitrobenzyl chloride in the usual manner and crystallised from benzene, forming pale yellow needles (9 g.), m. p. 109° (Found: C, 61·8; H, 5·1; N, 4·9; OMe, 21·9. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2; N, 4·8; OMe, 21·5%). Produced by reduction of this nitro-compound (11·6 g.)

[11] Hurtley, *J.*, 1929, 1870.

with sodium polysulphide, 2-*aminobenzyl* 3 : 4-*dimethoxyphenyl ether* formed needles (2·5 g.), m. p. 71°, from benzene–light petroleum (60—80°) (Found: C, 69·7; H, 6·5; N, 5·2. $C_{15}H_{17}O_3N$ requires C, 69·5; H, 6·6; N, 5·4%).

3 : 4-*Dimethoxybenzyl* 2-*Nitrophenyl Ether*.—*o*-Nitrophenol (25 g.) and veratroyl chloride (30 g.) interacted, forming 3 : 4-*dimethoxybenzyl* o-*nitrophenyl ether* which separated from benzene–light petroleum (b. p. 60—80°) in pale yellow needles (32 g.), m. p. 85° (Found: C, 62·1; H, 5·5; N, 5·5. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2; N, 4·8%). This ether (20 g.) was reduced with sodium polysulphide, to yield 2-*aminophenyl* 3 : 4-*dimethoxybenzyl ether*, needles (14 g.), m. p. 81° (from benzene) (Found: C, 69·2; H, 6·6; N, 5·5. $C_{15}H_{17}O_3N$ requires C, 69·5; H, 6·6; N, 5·4%). The *acetyl derivative* had m. p. 103° (Found: N, 4·6. $C_{17}H_{19}O_4N$ requires N, 4·7%).

Benzyl 4 : 5-*Dimethoxy*-2-*nitrophenyl Ether*.—By the standard method, 4-hydroxy-5-nitroveratrole (13·5 g.) gave the *ether* (16 g.) which separated from ethyl acetate in needles, m. p. 143° (Found: C, 62·0; H, 5·1; N, 4·9. $C_{15}H_{15}O_5N$ requires C, 62·3; H, 5·2; N, 4·8%), and when reduced by sodium polysulphide supplied 2-*amino*-4 : 5-*dimethoxyphenyl benzyl ether* (45% yield), crystallising from chloroform–light petroleum (b. p. 60—80°) in needles, m. p. 78°, which became pink in air (Found: N, 5·1. $C_{15}H_{17}O_3N$ requires N, 5·4%).

4-*Methoxybenzyl* 2-*Nitrophenyl Ether*.—Interaction of *o*-nitrophenol (20 g.) and 4-methoxybenzyl chloride (20 g.) gave the *ether* (13 g.) which crystallised from light petroleum (b. p. 60—80°) in pale yellow plates, m. p. 96° (Found: C, 65·2; H, 5·2; N, 5·4; OMe, 10·2. $C_{14}H_{13}O_4N$ requires C, 64·9; H, 5·1; N, 5·4; OMe, 12·0%). Reduced by sodium polysulphide, this nitro-compound (10 g.) furnished 2-*aminophenyl* 4-*methoxybenzyl ether* (6·5 g.) which on purification from chloroform–light petroleum (b. p. 60—80°) had m. p. 103° (Found: C, 73·6; H, 6·6; N, 6·2; OMe, 13·0. $C_{14}H_{15}O_2N$ requires C, 73·3; H, 6·6; N, 6·1; OMe, 13·5%). The *acetyl derivative* had m. p. 126° (Found: C, 70·7; H, 6·0; N, 5·2; OMe, 9·3. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3; N, 5·2; OMe, 11·4%).

3′ : 4′ : 5′ : 6′-*Tetrahydro*-2-*hydroxy*-2′-*hydroxymethyl*-4-*methoxydiphenyl*.—7 : 8 : 9 : 10-Tetrahydro-3-methoxybenzo[*c*]coumarin (11·5 g.) in dry ether (300 ml.) was added to lithium aluminium hydride (4 g.) in stirred ether, and the resulting *diol* (8·5 g.) crystallised from light petroleum (b. p. 60—80°)–methanol, forming needles, m. p. 81°, soluble in aqueous sodium hydroxide and having a violet ferric reaction (Found: C, 72·4; H, 7·6. $C_{14}H_{18}O_3$ requires C, 71·8; H, 7·7%). The *di*-p-*nitrobenzoate* formed pale yellow plates, m. p. 126° (Found: C, 62·6; H, 4·0; N, 5·5. $C_{28}H_{24}O_9N_2$ requires C, 63·2; H, 4·5; N, 5·3%).

2-*Hydroxy*-2′-*hydroxymethyl*-5-*methyldiphenyl* was prepared by the reduction of 2-methylbenzo[*c*]coumarin (6 g.) with lithium aluminium hydride in the usual manner and formed rods (5·5 g.), m. p. 94—95°, from benzene (Found: C, 78·4; H, 6·6. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6%). The *di*-p-*nitrobenzoate* had m. p. 137—138° (Found: C, 65·6; H, 4·1; N, 5·5. $C_{28}H_{20}O_8N_2$ requires C, 65·6; H, 3·9; N, 5·5%).

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[*Received, July 23rd*, 1957.]

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308. *Peroxides of Elements Other than Carbon. Part I. The Preparation and Reactions of Peroxysilanes.*

By E. Buncel and Alwyn G. Davies.

From the nucleophilic reaction of alkyl hydroperoxides with chlorosilanes a number of organoperoxysilanes, $R_{4-n}Si(O{\cdot}OR')_n$, have been isolated. Hydrogen peroxide similarly gives disilyl peroxides, but perbenzoic acid gives alkoxysilyl benzoates rather than alkylsilyl perbenzoates; the mechanism of this rearrangement is discussed.

Two main types of reaction, illustrated in equations (1) and (2), have been used for the preparation of organic peroxides. The first is a nucleophilic substitution,[1] the second is generally homolytic, and is frequently a chain reaction.[2]

$$RO{\cdot}OH + R'X \longrightarrow RO{\cdot}OR' + HX \quad . . . . . (1)$$
(R = H or alkyl; R′ = alkyl or acyl; X = an electronegative group)

$$O_2 + RR' \longrightarrow RO{\cdot}OR' \quad . . . . . (2)$$
(R = alkyl; R′ = H or alkyl)

Only diaryl peroxides have been prepared by the pairing of two oxygen radicals (eqn. 3),[3] and there seems to be no unequivocal example of the formation of a peroxide bond by the attack of nucleophilic oxygen on electrophilic oxygen (eqn. 4):[4]

$$2ArO{\cdot} \rightleftharpoons ArO{\cdot}OAr \quad . . . . . (3)$$

$$RO^- + O(R')-X \longrightarrow RO{\cdot}OR' + X^- \quad . . . . . (4)$$

This series of papers will describe attempts to extend reactions of these types to the preparation of peroxides of elements other than carbon.

The Preparation of Peroxysilanes.—The similarity of the chemistry of carbon and of silicon compounds and the ready availability of many organosilanes led us to investigate the reaction between chlorosilanes and alkyl hydroperoxides (eqn. 5).[5] The reaction takes place readily in ether or pentane in presence of pyridine, triethylamine, or ammonia.

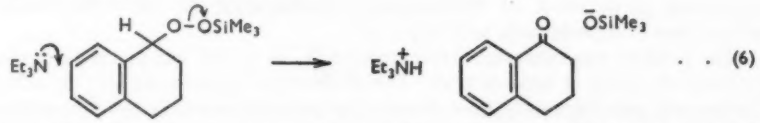
$$R_{4-n}SiCl_n + nR'O{\cdot}OH \longrightarrow R_{4-n}Si(O{\cdot}OR')_n + nHCl \quad . . . . . (5)$$
(n = 1—4)

The hydrochloride of the base is precipitated and from the filtrate the peroxysilane can be isolated in good yield. The use of ammonia is preferable to that of pyridine since pyridinium chloride is incompletely precipitated and tends to distil with the peroxysilane. The salt was sometimes removed by water but care must be taken not to hydrolyse the peroxysilane. By this method, eleven alkylperoxysilanes have been prepared and characterised; typical examples are trimethyl-(αα-dimethylbenzylperoxy)silane, triphenyl-(*tert.*-butylperoxy)silane, trimethyl-(1 : 2 : 3 : 4-tetrahydro-1-naphthylperoxy)silane, methyltri-(*tert.*-butylperoxy)silane, and tetra-(*tert.*-butylperoxy)silane. Trimethyl-(*tert.*-butylperoxy)silane was also obtained from the hydroperoxide and hexamethyldisilazine, but trimethylmethoxysilane was unreactive.

The peroxide structure of these compounds is well established. They are stable for some months at room temperature, but catalyse the polymerisation of styrene and of methyl methacrylate, and may detonate on local heating. They oxidise iodide to iodine quantitatively,

[1] Davies, *Adv. Catalysis*, 1957, **9**, 359.
[2] Frank, *Chem. Reviews*, 1950, **46**, 155; Hock and Kropf, *Angew. Chem.*, 1957, **69**, 313.
[3] References are given by Dimroth and Neubauer, *ibid.*, p. 95.
[4] But see Bladon, *J.*, 1955, 2176; Levitt, *Canad. J. Chem.*, 1953, **31**, 915; Levitt and Malinowski, *J. Amer. Chem. Soc.*, 1955, **77**, 4517.
[5] Buncel and Davies, *Chem. and Ind.*, 1956, 1052.

and are readily hydrolysed to the corresponding silanol and hydroperoxide. The infrared absorption spectra of trimethyl-(*tert.*-butylperoxy)silane and tetra-(*tert.*-butylperoxy)silane show strong absorption at 11·56 μ and 11·65 μ respectively, ascribed to the oxygen–oxygen stretching frequency. Trimethyl-(1 : 2 : 3 : 4-tetrahydro-1-naphthylperoxy)silane, in common with other primary and secondary alkyl peroxides,[6] undergoes base-catalysed decomposition forming the corresponding ketone:



. . (6)

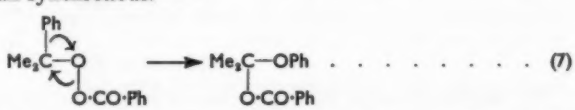
Disilyl peroxides are similarly prepared from chlorosilanes and hydrogen peroxide. Triphenylchlorosilane gave triphenylsilyl peroxide, but unlike triphenylmethyl peroxide or any of the alkylperoxysilanes it is unstable and the peroxide content drops to zero in a few days. In an attempt to prepare trimethylsilyl peroxide similarly the product detonated on distillation and this discouraged attempts to prepare similar compounds.

Meanwhile, three reports appeared of the preparation of silicon peroxides. Hahn and Metzinger [7] described the preparation of trimethyl-(*tert.*-butylperoxy)silane, trimethylsilyl hydroperoxide, and trimethylsilyl peroxide from chlorosilanes and *tert.*-butyl hydroperoxide or hydrogen peroxide in the presence of pyridine. They find that trimethylsilyl peroxide is stable to 135°, but that the hydroperoxide disproportionates readily into the disilyl peroxide and hydrogen peroxide, and decomposes with rapid evolution of oxygen above 35° under vacuum. This hydroperoxide may have been the cause of the detonation during our preparation of the disilyl peroxide.

Jenker [8] found that diethyldifluorosilane was oxidised by 100% hydrogen peroxide in presence of ammonia giving the ethoxysilane. The corresponding dichlorosilane gave a polymeric silyl peroxide containing some ethoxide and siloxane groups; these reactions are discussed later.

A patent [9] reports the formation of silicon peroxides by chlorosilanes and silanols with hydrogen peroxide. The formation of triphenyl- and triethyl-silyl peroxide by reaction of chlorine with the appropriate sodium siloxane is also described. This reaction, which has no analogy in the formation of dialkyl peroxides, presumably proceeds by the mechanism outlined in equation (3) or (4).

Oxygen–Oxygen Heterolysis in Peroxysilanes.—Tertiary alkyl peroxides undergo acid-catalysed oxygen–oxygen heterolysis by a nucleophilic 1 : 2-rearrangement; [10] *e.g.* equation (7) for αα-dimethylbenzyl perbenzoate.[11] In these rearrangements the bond-fission and bond-formation processes are all synchronous.[10a, 12]



. . . . . (7)

A number of nucleophilic 1 : 2-rearrangements from carbon to silicon are also recorded: Whitmore and his co-workers [13] showed electrophilic catalysis at the migration terminus

[6] Kornblum and de la Mare, *J. Amer. Chem. Soc.*, 1951, **73**, 880.
[7] Hahn and Metzinger, *Makromol. Chem.*, 1956, **21**, 113.
[8] Jenker, *Z. Naturforsch.*, 1956, **11b**, 757.
[9] U.S.P. 2,692,887; *Chem. Abs.*, 1955, **49**, 13,290.
[10] (*a*) Criegee, *Annalen*, 1948, **560**, 127; (*b*) Robertson and Waters, *J.*, 1948, 1574; (*c*) Reviewed by Leffler, *Chem. Reviews*, 1949, **45**, 385; "The Reactive Intermediates of Organic Chemistry," Interscience Publishers, New York, 1956, p. 166.
[11] Hock and Kropf, *Ber.*, 1955, **88**, 1544.
[12] Denney, *J. Amer. Chem. Soc.*, 1955, **77**, 1706; 1956, **78**, 590; Bassey, Bunton, Davies, Lewis, and Llewellyn, *J.*, 1955, 2471.
[13] Whitmore, Sommer, and Gould, *J. Amer. Chem. Soc.*, 1947, **69**, 1976; Sommer, Bailey, Gould, and Whitmore, *ibid.*, 1954, **76**, 801; Sommer and Evans, *ibid.*, p. 1186.

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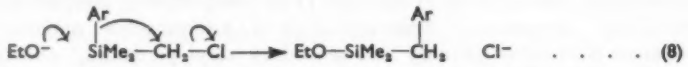
and Eaborn and Jeffrey [14] established an example of rearrangement initiated by nucleophilic attack at the migration origin (eqn. 8).



(8)

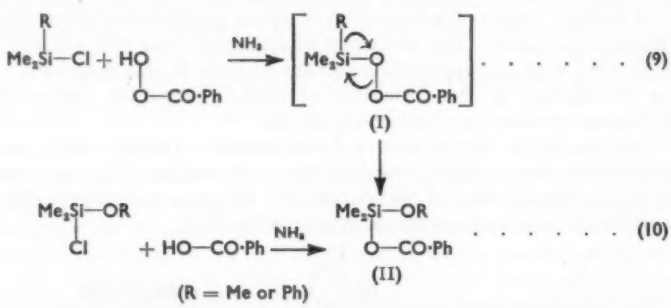
We observed nucleophilic migration of alkyl groups from silicon to oxygen in the attempted preparation of trimethylsilyl perbenzoate (I; R = Me) from trimethylchlorosilane and perbenzoic acid (eqn. 9).[15]

The product was isomeric with compound (I; R = Me) but was not a peroxide and was hydrolysed readily to benzoic acid. It was identified as the ester (II; R = Me) which was synthesised unambiguously from dimethylmethoxychlorosilane and benzoic acid (eqn. 10).

In support of the suggested mechanism, dimethylphenylchlorosilane with peroxybenzoic acid gave dimethylphenoxysilyl benzoate (II; R = Ph), the phenyl group migrating instead of the methyl group. This relative migration order is the same as that observed previously in carbon to carbon,[16] silicon to carbon,[14] and carbon to oxygen [10c,17] nucleophilic rearrangements, and differs from that found in homolysis of alkoxy-radicals.[18]

The stability of silylperoxy- and the corresponding alkylperoxy-esters can be compared. *tert.*-Butyl perbenzoate is stable below about 100°,[19] but during 15 minutes in boiling chloroform containing a trace of perchloric acid it decomposes giving acetone (82%) and benzoic acid (95%).[20] αα-Dimethylbenzyl per-esters are much less stable and have only recently been prepared; [11,20] on warming,[11] or with a trace of acid,[20] rearrangement readily takes place according to eqn. 7. The replacement of the carbon atom by a silicon atom therefore makes the ester more susceptible to rearrangement.

An attempt was made to prepare trimethoxysilyl perbenzoate by a reaction of the type shown in equation (9); rearrangement of this compound would involve the unfamiliar nucleophilic attack of oxygen on oxygen (eqn. 4), and the product would still be a peroxide. However, although trimethoxy-(*tert.*-butylperoxy)silane was readily prepared by the usual method, we were not able to isolate the corresponding perbenzoate.



(9)

(10)

The action of acidic hydrogen peroxide on dimethylphenylchlorosilane gave phenol, presumably by rearrangement of the intermediate hydroperoxide, but a similar acid-catalysed rearrangement of triphenyl-(*tert.*-butylperoxy)silane, or a base-catalysed rearrangement of dimethylphenyl-(*tert.*-butylperoxy)silane was not observed. The rearrangement [8] of the ethylsilylperoxy-structure to the ethoxysiloxy-structure may proceed by the mechanism described.

[14] Eaborn and Jeffrey, *J.*, 1957, 137.
[15] Buncel and Davies, *Chem. and Ind.*, 1957, 492.
[16] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 473; *J.*, 1953, 2845.
[17] Kharasch, Fono, and Nudenberg, *J. Org. Chem.*, 1950, **15**, 775.
[18] *Idem*, *ibid.*, p. 763.
[19] Milas and Surgenor, *J. Amer. Chem. Soc.*, 1946, **68**, 642.
[20] Davies and Nery, unpublished work; Davies and Moodie, *Chem. and Ind.*, 1957, 1622.

It is apparent that these nucleophilic rearrangements will be widespread in the chemistry of the peroxides of elements other than carbon, and may prevent the isolation of some of these compounds. For example, peroxides oxidatively dealkylate [21] organoboron compounds by a rearrangement of this kind, and a similar mechanism probably applies in the reduction of peroxides with Grignard reagents.[22] If such reduction can be avoided, the autoxidation of an organometallic or organometalloid compound will yield a peroxide [23] (cf. eqn. 2). Preparations of this type will be described later.

Experimental

General.—Certain operations involving peroxides, such as the mixing of reaction components and the distillation of products, were performed behind a " Perspex " safety screen, and whenever possible the products were not heated above 100°. Samples of diethyldi-(*tert.*-butylperoxy)silane and of tetra-(*tert.*-butylperoxy)silane exploded while being sealed for analysis.

Analytical.—Silicon. The compound (0·1—0·2 g.) in a silica beaker (8 cm. high, 2·5 cm. diam.) was covered with chlorobenzene (0·3 c.c.) to moderate the subsequent reaction. Concentrated sulphuric acid (1·5 c.c.) and nitric acid (0·5 c.c.) were added and the mixture gently heated until it solidified. The silica was then ignited to constant weight at 800°.

Volatile liquids were weighed into a gelatin capsule which was placed in a small test-tube, and the whole transferred to a Carius tube containing the mixed acids. The tube was sealed, the contents mixed, and the whole heated in a furnace at 240° for 6 hr. The contents were washed quantitatively into a weighed platinum beaker and ignited to silica as above.

Peroxidic oxygen. The sample (0·1—0·2 g.), glacial acetic acid (5 c.c.), and saturated sodium iodide (5 c.c.) were added successively to *iso*propyl alcohol (50 c.c.). The mixture was kept overnight in the dark. Next day the liberated iodine was titrated with 0·1N-sodium thiosulphate. A blank estimation was run concurrently.

Carbon and hydrogen. Samples of peroxysilanes usually exploded in the combustion train, although they were carefully heated in a stream of air at reduced pressure rather than in oxygen. It was difficult to obtain reproducible analytical results on the same specimen, particularly for carbon.

Preparation of Organoperoxysilanes.—(i) *Trimethyl-*(tert.-*butylperoxy*)*silane.* (*a*) A solution of *tert.*-butyl hydroperoxide (2·70 g.) and pyridine (2·37 g.) in pentane (20 c.c.) was added at 0° to a solution of trimethylchlorosilane (3·34 g.) in pentane (20 c.c.). Pyridinium chloride (3·54 g.) was immediately precipitated. Distillation of the filtrate yielded trimethyl-(*tert.*-butylperoxy)silane (4·33 g.), b. p. 79°/215 mm., n_D^{25} 1·3935, d_D^{25} 0·8219 (Found: C, 52·6; H, 11·3; Si, 16·6; peroxidic O, 9·45%; *M*, 159. Calc. for $C_7H_{18}O_2Si$: C, 51·8; H, 11·2; Si, 17·3; peroxidic O, 9·85%; *M*, 162). Hahn and Metzinger report b. p. 41°/41 mm., d^{20} 0·798, n^{20} 1·3933.

The same product was obtained in 60% yield in the absence of pyridine.

(*b*) A mixture of hexamethyldisilazine (1·61 g.) and *tert.*-butyl hydroperoxide (1·80 g.) in ether (35 c.c.) was heated under reflux for 9 hr., and was then distilled, giving three fractions all of b. p. 39°/40 mm., but with n_D^{25} 1·3891, 1·3906, and 1·3914 (Found for the final fraction: C, 51·6; H, 11·0; peroxidic O, 9·67%).

An attempt to carry out a similar reaction with methoxytrimethylsilane led to its recovery, b. p. 57°, n_D^{25} 1·3653.

(ii) *Trimethyl-*(tert.-*pentylperoxy*)*silane.* From *tert.*-pentyl hydroperoxide (4·42 g.), pyridine (3·56 g.), and trimethylchlorosilane (4·59 g.) in pentane (60 c.c.) at 0°, *trimethyl-*(tert.-*pentylperoxy*)*silane* (6·18 g.) was obtained, b. p. 78°/95 mm., n_D^{25} 1·4032, d_4^{25} 0·8419 (Found: C, 55·4; H, 11·4; Si, 15·6; peroxidic O, 9·1%; *M*, 174. $C_8H_{20}O_2Si$ requires C, 54·5; H, 11·4; Si, 15·9; peroxidic O, 9·1%; *M*, 176).

(iii) *Trimethyl-*(αα-*dimethylbenzylperoxy*)*silane.* A mixture of αα-dimethylbenzyl hydroperoxide (3·04 g.), pyridine (1·58 g.), and trimethylchlorosilane (2·16 g.) in pentane (40 c.c.) at 0° gave a precipitate of pyridinium chloride (2·25 g.). The filtrate was washed rapidly with ice-cold water, dried (Na_2SO_4), and distilled, yielding *trimethyl-*(αα-*dimethylbenzylperoxy*)*silane*

[21] Kuivila, *J. Amer. Chem. Soc.*, 1954, **76**, 870; R. Moodie, unpublished work.
[22] Walling and Buckler, *ibid.*, 1955, **77**, 6032.
[23] Anderson, *ibid.*, 1952, **74**, 2371.

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(2·20 g.), b. p. 43°/0·05 mm., n_D^{25} 1·4780, d_4^{25} 0·9501 (Found: C, 64·5; H, 9·1; Si, 11·9; peroxidic O, 7·4. $C_{13}H_{20}O_2Si$ requires C, 64·3; H, 9·0; Si, 12·5; peroxidic O, 7·1%).

(iv) *Trimethyl-*(1 : 2 : 3 : 4-*tetrahydro*-1-*naphthylperoxy*)*silane.* Dry ammonia was passed for 30 min. through a solution of 1 : 2 : 3 : 4-tetrahydro-1-naphthyl hydroperoxide (3·28 g.) and trimethylchlorosilane (2·16 g.) in ether (30 c.c.) at 0°. Ammonium chloride (0·46 g.) was filtered off; the filtrate yielded *trimethyl-*(1 : 2 : 3 : 4-*tetrahydro*-1-*naphthylperoxy*)*silane* (4·61 g.), b. p. 53°/0·01 mm., n_D^{25} 1·5102, d_4^{25} 1·015 (Found: C, 65·4; H, 8·4; Si, 11·0; peroxidic O, 7·0. $C_{13}H_{20}O_2Si$ requires C, 66·0; H, 8·5; Si, 11·9; peroxidic O, 6·8%).

(v) *Triphenyl-*(tert.-*butylperoxy*)*silane.* A solution of *tert.*-butyl hydroperoxide (0·90 g.) and triphenylchlorosilane (2·94 g.) in ether (30 c.c.) was treated as in (iv), yielding ammonium chloride (0·45 g.). The filtrate was evaporated to dryness, and the residue recrystallised from pentane yielding *triphenyl-*(tert.-*butylperoxy*)*silane* (2·71 g.), m. p. *ca.* 50° (Found: C, 76·2; H, 6·9; Si, 8·0; peroxidic O, 4·5. $C_{22}H_{24}O_2Si$ requires C, 75·8; H, 6·9; Si, 8·05; peroxidic O, 4·6%).

(vi) *Dimethylphenyl-*(tert.-*butylperoxy*)*silane.* A solution of *tert.*-butyl hydroperoxide (2·96 g.) and dimethylphenylchlorosilane (5·60 g.) in ether (80 c.c.), was treated as in (iv), yielding ammonium chloride (1·47 g.) and a liquid (6·55 g.) which was distilled in a molecular still from a bath at 45—55°. The following fractions were collected: (*a*) 3 c.c., b. p. 40°/0·05 mm., n_D^{25} 1·4762; (*b*) 2 c.c., b. p. 50°/0·05 mm., n_D^{25} 1·4748; (*c*) <0·5 c.c., b. p. 50°/0·001 mm., n_D^{25} 1·4885 [Found: peroxidic O, (*a*) 6·85, (*b*) 6·75, (*c*) 3·06%]. A non-volatile residue (*ca.* 0·5 c.c.) remained. The first fraction consisted of impure dimethylphenyl-(*tert.*-butylperoxy)silane (Found: C, 62·8; H, 8·9; peroxidic O, 6·8. $C_{12}H_{20}O_2Si$ requires C, 64·3; H, 9·0; peroxidic O, 7·1%).

(vii) *Trimethoxy-*(tert.-*butylperoxy*)*silane.* All manipulations of trimethoxysilyl compounds were conducted in the dry box. Dry ammonia was passed for 45 min. through a solution of *tert.*-butyl hydroperoxide (1·10 g.) and trimethoxychlorosilane (1·92 g.) in ether (40 c.c.) at 0°, yielding ammonium chloride (0·63 g.; calc. 0·65 g.) and a liquid residue (2·33 g.) which gave *trimethoxy-*(tert.-*butylperoxy*)*silane*, b. p. 49°/6 mm. (Found: C, 40·1; H, 8·9; Si, 13·5; peroxidic O, 7·25. $C_7H_{16}O_5Si$ requires C, 40·0; H, 8·6; Si, 13·4; peroxidic O, 7·6%).

Two attempts to prepare trimethoxysilyl perbenzoate by a similar method from perbenzoic acid did not give any clearly defined product. From both experiments a liquid was obtained in poor yield, b. p. 50° (bath)/0·001 mm., which had a very low peroxide content and an analysis corresponding roughly to that of trimethoxysilanol ($C_3H_{10}O_4Si$).

(viii) *Diethyldi-*(tert.-*butylperoxy*)*silane.* A solution of *tert.*-butyl hydroperoxide (5·40 g.), diethyldichlorosilane (4·71 g.), and pyridine (4·74 g.) in pentane (60 c.c.) yielded *diethyldi-*(tert.-*butylperoxy*)*silane* (4·82 g.), b. p. 40°/1 mm., n_D^{25} 1·4149, d_4^{25} 0·9415 (Found: C, 55·1; H, 10·7; Si, 11·1; peroxidic O, 11·8%; *M*, 257. $C_{12}H_{28}SiO_4$ requires C, 54·5; H, 10·7; Si, 10·6; peroxidic O, 12·1%; *M*, 264).

(ix) *Diphenyldi-*(tert.-*butylperoxy*)*silane.* *tert.*-Butyl hydroperoxide (3·77 g.), pyridine (3·31 g.), diphenyldichlorosilane (5·30 g.), and pentane (50 c.c.) were mixed at 0°. Next day the precipitate of pyridinium chloride was removed (4·50 g.); the filtrate yielded *diphenyldi-*(tert.-*butylperoxy*)*silane* as a viscous liquid, b. p. 110°/0·001 mm., n_D^{25} 1·5103, d_4^{25} 1·033 (Found: C, 66·7; H, 7·7; Si, 6·95; peroxidic O, 8·7. $C_{20}H_{28}SiO_4$ requires C, 66·6; H, 7·8; Si, 7·8; peroxidic O, 8·9%).

(x) *Methyltri-*(tert.-*butylperoxy*)*silane.* Similarly, a mixture of *tert.*-butyl hydroperoxide (8·10 g.), pyridine (7·11 g.), and methyltrichlorosilane (4·50 g.) in pentane (60 c.c.) at 0°, yielded *methyltri-*(tert.-*butylperoxy*)*silane* (4·56 g.), b. p. 50°/0·1 mm., n_D^{25} 1·4097 (Found: C, 51·2; H, 10·1; Si, 9·4%; *M*, 307. $C_{13}H_{30}SiO_6$ requires C, 50·3; H, 9·75; Si, 9·0%; *M*, 310).

(xi) *Tetra-*(tert.-*butylperoxy*)*silane.* *tert.*-Butyl hydroperoxide (7·18 g.) in ether (75 c.c.) was added (dry box) to silicon tetrachloride (3·27 g.) and dry ammonia was passed through the solution for 1 hr. at 0°. The precipitate of ammonium chloride (4·00 g.; calc. 3·98 g.) was filtered off, and the filtrate evaporated. Vacuum sublimation at 0·001 mm. of the residue (7·20 g.) from a bath at 50° gave fine white crystals of *tetra-*(tert.-*butylperoxy*)*silane*, m. p. (sealed tube) 35—40° (Found: C, 50·2; H, 9·8%; *M*, 379. $C_{16}H_{36}O_8Si$ requires C, 50·0; H, 9·4; Si, 73%; *M*, 384).

Similarly the hydroperoxide (7·20 g.), pyridine (6·32 g.), and silicon tetrachloride (3·38 g.) in pentane (60 c.c.) at 0° gave pyridinium chloride and the silyl peroxide (Found: C, 50·6; H, 9·7; Si, 7·7%; *M*, 377). Determination of the peroxidic oxygen gave erratic, but approximately correct, results.

Attempts to prepare the peroxide by treating tetramethoxysilane with *tert.*-butyl hydroperoxide were not successful. The presence of an acid ion-exchange resin as catalyst led to hydrolysis of the tetramethoxysilane; the use of hydrogen chloride caused alkyl–oxygen heterolysis of the hydroperoxide giving principally *tert.*-butyl chloride and *tert.*-butyl peroxide, identified by vapour-phase chromatography and infrared absorption spectra.

Experiments on Disilyl Peroxides.—(i) *Trimethylsilyl peroxide.* A solution of 87% hydrogen peroxide (1·56 g.) and trimethylchlorosilane (4·32 g.) in ether (20 c.c.) at 0° was kept for 16 hr. in a desiccator containing solid potassium hydroxide. The ether was removed and distillation continued at 260 mm. Liquid began to distil, b. p. 36°; this temperature gradually rose to 55° whereupon a violent explosion occurred.

(ii) *Triphenylsilyl peroxide.* From a similar experiment with triphenylchlorosilane it was recovered, m. p. and mixed m. p. 90—92°; similarly no peroxide could be isolated from the interaction of triphenylsilanol and hydrogen peroxide in acetic acid or acetic acid–sulphuric acid.

After 2 hr., pentane (20 c.c.) was added to a solution of 87% hydrogen peroxide (0·08 g.), pyridine (0·16 g.), and triphenylchlorosilane (0·59 g.) in ether (15 c.c.) at 0°. Pyridinium chloride (0·24 g.) was precipitated. The filtrate was washed rapidly with water and dried (Na_2SO_4) yielding a white crystalline solid (0·48 g.), m. p. *ca.* 85° (Found: peroxidic O, 4 hr. after start of reaction: 1·8%; after 91 hr., 0·2%).

The reaction was therefore repeated as rapidly as possible on twice the above scale (Found: peroxidic O, after 1·5 hr., 2·1%; after 21 hr., 0·9%; C, 78·1; H, 6·1%). After several weeks the m. p. of the solid was 130° (Found: C, 77·9; H, 6·0%). *Triphenylsilyl peroxide* ($C_{36}H_{30}Si_2O_2$) requires C, 78·5; H, 5·5; peroxidic O, 2·9%.

*Reduction of Trimethyl-(*tert.*-butylperoxy)silane.*—The peroxysilane (5·0 g.) was shaken for 5 hr. with aqueous sodium sulphite heptahydrate (8·5 g.; 2·5 mol.). A pentane extract yielded two main fractions: (i) b. p. 82—89°, n_D^{25} 1·3797; (ii) b. p. 89—95°, n_D^{25} 1·3848. It is known that trimethylsilanol (b. p. 99°, n_D^{20} 1·3880) with hexamethyldisiloxane (b. p. 100°, n_D^{25} 1·3748) forms a binary azeotrope (b. p. 89—91°, n_D^{20} 1·3800). Fractions (i) and (ii) combined were therefore heated under reflux with 6N-hydrochloric acid for 1 hr. A pentane extract yielded hexamethyldisiloxane, b. p. 98°, n_D^{25} 1·3752.

The aqueous solution from the reduction was distilled giving as a first fraction the *tert.*-butyl alcohol–water azeotrope, from which *tert.*-butyl alcohol was salted out with potassium chloride.

Silicon–Oxygen Heterolysis in Peroxysilanes.—(i) Trimethyl-(*tert.*-butylperoxy)silane (0·49 g.) and triphenylmethanol (0·78 g.) were dissolved in acetic acid (100 c.c.) containing sulphuric acid (0·1 c.c.). Next day the mixture was poured on ice, and the precipitate (0·83 g.) recrystallised from ethanol giving *tert.*-butyl triphenylmethyl peroxide (0·34 g.), m. p. and mixed m. p. 69—71°.

(ii) Trimethyl-(*tert.*-pentylperoxy)silane (0·35 g.) and xanthhydrol were dissolved in acetic acid (10 c.c.). Next day, *tert.*-pentyl 9-xanthenyl peroxide (recrystallised, 0·42 g.) was isolated, m. p. 39°.

(iii) Trimethyl-(αα-dimethylbenzylperoxy)silane (0·22 g.) and xanthhydrol (0·20 g.) in acetic acid yielded αα-dimethylbenzyl 9-xanthenyl peroxide (recrystallised, 0·20 g.), m. p. and mixed m. p. 96—97°.

Oxygen–Oxygen Heterolysis in Peroxysilanes.—(i) *The reaction of trimethylchlorosilane with perbenzoic acid.* Dry ammonia was passed through a solution of 80% perbenzoic acid (5·48 g.) and trimethylchlorosilane (6·48 g.) in ether (80 c.c.) for 30 min. at 0°. After 16 hr. the precipitate of ammonium chloride and ammonium benzoate (2·75 g.) was filtered off. Distillation of the filtrate gave two fractions: (*a*) b. p. 40—42°/0·1 mm., n_D^{25} 1·4817; and (*b*) b. p. 33—36°/0·01 mm., n_D^{25} 1·4810.

Fraction (*a*) was non-peroxidic. It was hydrolysed readily in the air and was identified as trimethylsilyl benzoate [Found: C, 61·5; H, 7·2; Si, 13·4%; *M* (by titration with NaOH), 200. Calc. for $C_{10}H_{14}O_2Si$: C, 61·8; H, 7·3; Si, 14·4%; *M*, 194]. Anderson [23] reports b. p. 221°/760 mm.

Fraction (*b*) was also non-peroxidic and was hydrolysed readily. Elementary analysis showed it to be *dimethylmethoxysilyl benzoate* (II; R = Me) (Found: C, 57·2; H, 6·8; Si, 13·0%; *M*, 207. $C_{10}H_{14}O_2Si$ requires C, 57·1; H, 6·7; Si, 13·4%; *M*, 210).

This was confirmed by an unambiguous preparation: The reaction between dimethylchlorosilane and methanol in pentane in the presence of ammonia gave dimethylmethoxychlorosilane. This (3·15 g.) and benzoic acid (3·05 g.) in ether (35 c.c.) were treated with ammonia for 30 min.

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at 0° yielding ammonium chloride (1·0 g.) and dimethylmethoxysilyl benzoate, b. p. 33—35°/0·01 mm. (Found: C, 56·7; H, 6·89%; *M*, 212).

(ii) *The reaction of dimethylphenylchlorosilane with perbenzoic acid.* By the usual method, dimethylphenylchlorosilane (3·42 g.) and perbenzoic acid (3·46 g.) in ether was treated with ammonia, giving a liquid (3·50 g.). Distillation gave *dimethylphenoxysilyl benzoate* (II; R = Ph), b. p. 50°/0·001 mm., n_D^{25} 1·5261 (Found: C, 66·6; H, 6·9. $C_{15}H_{16}O_3Si$ requires C, 66·2; H, 5·9%). Hydrolysis gave phenol in 66% yield (toluene-*p*-sulphonate, m. p. 93°), and benzoic acid, m. p. 120°.

Identity was confirmed by independent synthesis: Dimethyldichlorosilane (25 g.) and phenol (15·6 g.) in pentane–ether when treated with pyridine (13·2 g.) gave only *dimethyldiphenoxysilane*, b. p. 135°/6 mm. (Found: C, 68·3; H, 6·5; Si, 11·6. $C_{14}H_{16}O_2Si$ requires C, 68·8; H, 6·6; Si, 11·5%). However, when ammonia was passed through a solution of the dichlorosilane (50 g.) and phenol (32 g.) in ether (150 c.c.) for 1 hr. at 0°, dimethylphenoxychlorosilane (9·7 g.) was obtained, b. p. 200°/760 mm. (Found: Cl, 16·9. Calc. for $C_8H_{11}OClSi$: Cl, 18·8%), together with a considerable residue of dimethyldiphenoxysilane, b. p. 130—132°/5 mm.

Dimethylphenoxychlorosilane (3·78 g.) and benzoic acid (2·45 g.), by the ammonia method, gave dimethylphenoxysilyl benzoate, b. p. 50°/0·001 mm., n_D^{26} 1·5259 (Found: C, 65·7; H, 6·6%). Hydrolysis gave phenol (toluene *p*-sulphonate, m. p. 93°).

(iii) *The action of acidic hydrogen peroxide on dimethylphenylchlorosilane.* A solution of 87% hydrogen peroxide (0·50 g.) and dimethylphenylchlorosilane (1·71 g.) in glacial acetic acid (20 c.c.) containing concentrated sulphuric acid (0·05 c.c.) was kept for 48 hr., bromine was then added, and, after a further 20 min., the mixture was poured into water. The precipitate, which was reprecipitated on acidification of its solution in 2N-sodium hydroxide, was recrystallised from light petroleum; it then had m. p. 65°. It was identified as *p*-bromophenol by formation of its toluene-*p*-sulphonate, m. p. 93°.

(iv) *Action of base on trimethyl-*(1 : 2 : 3 : 4-*tetrahydro*-1-*naphthylperoxy*)*silane.* A solution of the peroxysilane (0·59 g.) in triethylamine (1·28 g.) became pink during 65 hr. at 35°. It yielded 1 : 2 : 3 : 4-tetrahydro-1-oxonaphthalene 2 : 4-dinitrophenylhydrazone (0·5 g.), m. p. and mixed m. p. 257°.

(v) *The action of acid on triphenyl-*(tert.-*butylperoxy*)*silane.* (*a*) The peroxysilane was recovered after being treated in pentane with a cation-exchange resin (acid form).

(*b*) Hydrogen chloride was passed into an ethereal solution of the peroxysilane; the exothermic reaction caused the ether to boil, and after 4 hr. it was removed. The residue was largely triphenylchlorosilane; no phenol could be isolated after hydrolysis.

(*c*) The peroxysilane (2·50 g.) was suspended in acetic acid (100 c.c.) containing sulphuric acid (0·3 c.c.). Next day, excess of sodium hydroxide was added, and the solution then saturated with carbon dioxide. An ethereal extract gave a moist mixture (2·10 g.), m. p. *ca.* 135°, of triphenylsilanol, m. p. 150°, and *tert.*-butyl hydroperoxide. No phenol could be detected.

(*d*) The peroxysilane was treated with aluminium chloride (up to 1 mol.) in pentane or benzene at 65° for periods of up to 3 hr. From all these experiments the peroxysilane was recovered and no phenol could be detected.

(vi) *The action of base on dimethylphenyl-*(tert.-*butylperoxy*)*silane.* (*a*) A solution of the peroxysilane (0·59 g.) and triethylamine (1·36 g.) in benzene (20 c.c.) was kept at 50° for 24 hr. and at 80° for 4 hr. The peroxysilane (0·63 g.) was recovered (Found: peroxidic O, 5·75%).

(*b*) A solution of the peroxysilane (0·57 g.), triethylamine (1·98 g.), and *tert.*-butyl hydroperoxide (1·06 g.) in benzene (20 c.c.) was kept at 50° for 6 days. Evacuation at 0·1 mm. left an oil (1·05 g.) containing some solid (Found, on the mixture: peroxidic O, 2·28%). The residue was heated at 100° for 1 hr. with 6N-hydrochloric acid (20 c.c.), then decolorised with charcoal. No phenol could be detected by the bromate–bromide method.

We are indebted to Professors E. D. Hughes, F.R.S., and C. K. Ingold, F.R.S., for their interest and encouragement, to Mr. G. Scott of Imperial Chemical Industries Limited, Dyestuffs Division, for many helpful discussions, and to Imperial Chemical Industries Limited, Nobel Division, and Laporte Chemicals Limited for the gift of chemicals.

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University College, Gower Street, London, W.C.1. [*Received, September 6th*, 1957.]

309. *The Conductivity of Silver Salts in Non-aqueous and Mixed Solvents. Part VI.*[1]

By V. S. Griffiths and M. L. Pearce.

The effects of *cyclo*pentadiene, di*cyclo*pentadiene, polystyrene, and benzene on the conductivity of silver perchlorate in acetone have been observed.

Silver ions are preferentially solvated by nitrogenous basic components of binary non-aqueous solvent mixtures.[1b-e] The extent of this depends upon the mobility of the π electrons on the nitrogen atom of the bases concerned. This property of silver ions was demonstrated conductometrically and accounted for on the basis of their electrophilic nature. Similar solvent–ion interaction occurs between silver ions and olefinic or aromatic solvents.[2,3] Conductometric measurements at 1500 cycles/sec. detected qualitatively an interaction between benzene and silver ions [1e] but the apparatus used was not sufficiently sensitive for quantitative measurements.

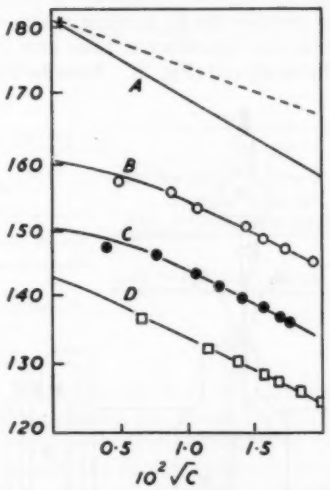

Fig. 1. *Equivalent conductivity of silver perchlorate in: A, pure acetone; B, 1% cyclopentadiene in acetone; C, 1% dicyclopentadiene in acetone; D, the polystyrene suspension. The broken line is the theoretical Onsager slope.*

It was felt that interaction involving an olefin might be measurable by this method if the molecular weight of compound was high enough for the mobility of any complex ions formed to be severely impaired. Polystyrene was chosen, as some specimens of this polymer, although theoretically saturated, do contain olefinic groups. Certain difficulties were encountered. Owing to the extremely low solubility of polystyrene in acetone the conductivity of " saturated " solutions, which were formed by prolonged shaking of polystyrene with pure acetone, was not reproducible. However, addition of a solution of polystyrene in benzene to a large excess (1 : 100) of acetone, gave a " fine suspension " of polystyrene. The conductivity of such mixtures was reproducible and although the system now unfortunately becomes more complex, the large effect of the addition of a benzene–polystyrene mixture on the conductivity of silver perchlorate in acetone is most striking in view of the extremely small effect of benzene.[1e]

Moffitt's theoretical investigations,[4] later confirmed by Pfab and Fischer [5] and Eiland

[1] (*a*) Part I, *J.*, 1954, 686; (*b*) Part II, *J.*, 1955, 1208; (*c*) Part III, *ibid.*, p. 2797; (*d*) Part IV, *J.*, 1956, 473; (*e*) Part V, *J.*, 1957, 3243.
[2] Winstein and Lewis, *J. Amer. Chem. Soc.*, 1938, **60**, 836.
[3] Taufen, Murray, and Cleveland, *ibid.*, 1941, **63**, 3500.
[4] Moffitt, *ibid.*, 1954, **76**, 3386.
[5] Pfab and Fischer, *Z. Naturforsch.*, 1952, **7b**, 377.

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and Pepinsky,[6] showed that " sandwich molecules " are formed between *cyclo*pentadiene and transition-element atoms which contain two vacant or singly occupied *d* orbitals. Although silver ions do not fulfil these electronic requirements, it was expected that some form of complex-ion formation should occur with *cyclo*pentadiene; study of di*cyclo*pentadiene should indicate whether this is of the " sandwich molecule " type. Hence the conductivity of silver perchlorate in the above polystyrene mixture and in 99% acetone–1% *cyclo*pentadiene and in 99% acetone–1% di*cyclo*pentadiene was investigated and compared with that in pure acetone [1e] (Fig. 1).

TABLE 1. *Dielectric constant* (ε), *equivalent conductivity at infinite dilution* (Λ_0), *Stokes radius* (r_+), *and Bjerrum parameter* (a) *determined as in Part V.*[1e]

Solvent	$10^4\varepsilon$	Λ_0	r_+ (Å)	a (Å)
Pure Acetone	5·4	181·5	2·86	2·14
1% *cyclo*Pentadiene	16·9	160	3·87	2·64
1% Di*cyclo*pentadiene	14·1	150	4·54	2·55
Polystyrene suspn.	26·2	143	3·66	9·46

We attempted to measure quantitatively the effect of benzene on the conductivity of silver perchlorate in acetone which was detected with a 1500 c./sec. bridge by using a 10,000 c./sec. transformer ratio-arm bridge [7] with an oscilloscope as detector, and a special conductivity cell (Fig. 2). In order rapidly to mix the benzene added to a solution of silver

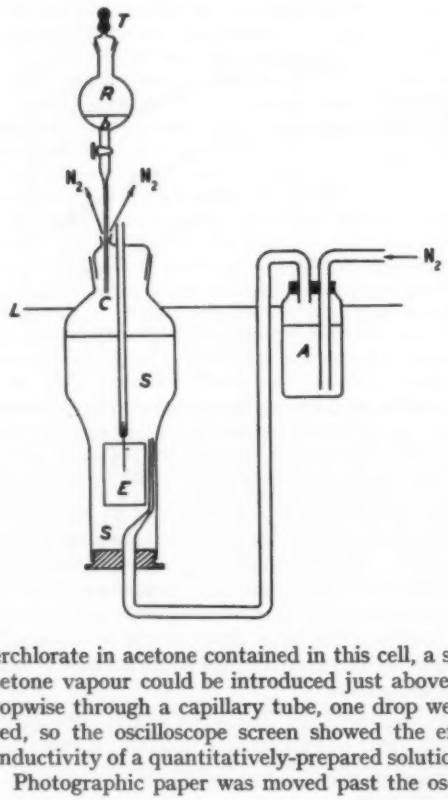


FIG. 2. *Apparatus: T, Rubber teat; R, reservoir; b, benzene; C, fine capillary; L, oil level in thermostat; S, solution; A, pure acetone; E, electrodes.*

perchlorate in acetone contained in this cell, a slow stream of nitrogen pre-saturated with acetone vapour could be introduced just above the electrodes. Benzene could be added dropwise through a capillary tube, one drop weighing 0·050 $\pm$ 0·0005 g. for the capillary used, so the oscilloscope screen showed the effect of a given mass of benzene on the conductivity of a quantitatively-prepared solution of silver perchlorate in acetone.

Photographic paper was moved past the oscilloscope screen by a powered camera to

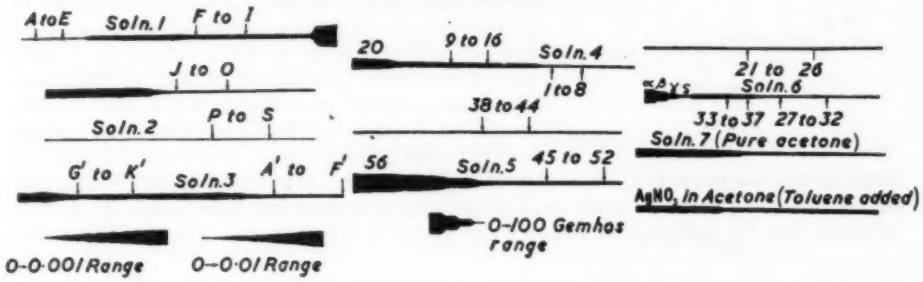
[6] Eiland and Pepinsky, *J. Amer. Chem. Soc.*, 1952, **74**, 4971.
[7] Calvert, Cornelius, Griffiths, and Stock, *J. Phys. Chem.*, 1958, **62**, 47.

record traces (Fig. 3) whose thickness, determined with a travelling microscope, measured the degree of " off balance " of the bridge and hence, by calibration, quantitative changes in conductivity.

*cyclo*Pentadiene, di*cyclo*pentadiene, and polystyrene all decrease Λ_0 and increase the dissociation constant of silver perchlorate in acetone. A comparison of the values of the dissociation constant, Λ_0, and Stokes's radii (Table 1) for the 1% *cyclo*pentadiene solution with those of a 1% pyridine solution [1e] indicates that the *cyclo*pentadienyl complex ion is the more bulky and that preferential solvation is more extensive in this solvent. Hence the *cyclo*pentadienyl complex ion probably contains more than one *cyclo*pentadiene molecule.

The effect of di*cyclo*pentadiene is also of interest. A greater decrease in Λ_0 is produced than for the monomer whereas the dissociation constant does not increase to the same extent. Thus it now appears that the di*cyclo*pentadienyl complex ion is more bulky than the *cyclo*pentadienyl ion and yet that preferential solvation of the latter is the more extensive. We have already deduced that the *cyclo*pentadienyl ion probably contains more than one organic molecule and if this applies to the dimer we should expect a larger, not smaller, dissociation constant for the latter. Hence it is most likely that the di*cyclo*-pentadienyl complex ion contains only one di*cyclo*pentadiene molecule and that the

FIG. 3. *Examples of photographic traces.*



relatively greater mobility of the *cyclo*pentadiene complex, which on this basis is of virtually the same mass, is due to easy packing of the monomeric molecules round the silver ion such as would occur for a " sandwich molecule " structure. This structure is further supported by r_+ and a for the two mixtures. Although the Stokes radius increases in going from the *cyclo*pentadiene to the di*cyclo*pentadiene complex, as is consistent with the conception of a compact rather than a diffuse complex, the values of the Bjerrum parameter are approximately the same. This is reasonable because the " sandwich molecule " structure shields the ion from approach in any direction whereas any structure formulated for a complex between one silver ion and one tricyclic, and hence necessarily uniplanar, molecule, must allow easy approach of the ion in at least one direction.

The complex nature of the conducting system in the polystyrene suspension makes the conclusions most tentative. Although the decrease in conductivity appears at first sight to be very large, closer examination, particularly of the unusually high dissociation constant, reveals that it is not so large as might be expected. This is reflected in the relative values of the Bjerrum parameter and Stokes radius, the former being exceptionally large in this solution. The decrease in conductivity may be partly due to the adsorption of silver ions on undissolved polymer particles. However this is at variance with the observation that large variations in the concentration of polystyrene in the solvent mixture had little or no effect on the decrease in conductivity. An alternative, more likely, explanation is that one polystyrene molecule can form a complex with more than one silver ion; one complex ion may be quite highly charged and this would so affect its mobility as to compensate partially for its large bulk. It will also be uncertain whether the Bjerrum

parameter measures the distance of closest approach of the large complex ions or the mean distance of separation of silver ions within the large complex ions.

The value of the conductometric results at 10,000 c./sec. for the effect of benzene and pyridine on silver perchlorate in acetone (Table 2; κ_1 and κ_f are the specific conductivities before and after addition of masses m_b or m_p of benzene or pyridine respectively and C the molar concentration of silver perchlorate) is impaired by the large errors involved. For example, although the maximum error involved in the gross conductivity measurements made was probably 0·05—0·5%, this becomes a possible error of 40% when a difference factor such as $\Delta\kappa_b$ is considered.

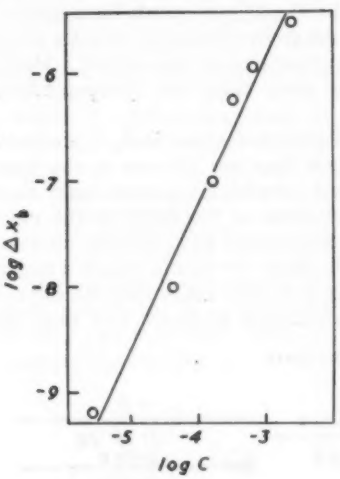


FIG. 4.

The decrease in conductivity observed when benzene is added to a solution of silver perchlorate in acetone being assumed to be due to the formation of stoicheiometric complex ions, the concentration of the ionic complex should depend linearly on the concentration of both benzene and silver ions. For present purposes this means that the decrease in conductivity caused by the benzene, $\Delta\kappa_b$, should be proportional to the concentration of silver ions, C, and, since the volumes of the solutions used were always the same to within 2 or 3%, to the mass of benzene added, m_b. Hence $\Delta\kappa_b/C$ and $\Delta\kappa_b/m_b$ should both be constant for all solutions used. Table 3 shows that although $\Delta\kappa_b/C$ is constant to within a factor of ten, $\Delta\kappa_b/m_b$ is not, since it varies by more than three thousandfold. Thus, the large errors being borne in mind, $\Delta\kappa_b/C$ is probably constant (see Fig. 4), and this merely indicates that the reduction in conductivity is due to a reduction in the mobility of the

TABLE 2.

Soln.	1*a*	1*b* *	2*a*	2*b* *	3	4	5	6	7 †
10^4C	17·13	17·13	64·39	64·39	280·9	30·54	3·927	0·253	0
m_b (g.) ...	0·220	0·0	0·356	0·220	0·238	0·238	0·238	0·238	0·238
m_p (g.) ...	0·05	0·05	0·05	0·10	0·10	0·10	0·10	0·50	0·10
κ_1	3·57 × 10^{-5}	3·56 × 10^{-5}	1·33 × 10^{-4}	1·35 × 10^{-4}	3·62 × 10^{-4}	4·97 × 10^{-5}	6·89 × 10^{-6}	5·58 × 10^{-7}	5·045 × 10^{-8}
κ_f	3·39 × 10^{-5}	3·39 × 10^{-5}	1·28 × 10^{-4}	1·28 × 10^{-4}	3·53 × 10^{-4}	4·71 × 10^{-5}	6·775 × 10^{-6}	5·63 × 10^{-7}	5·515 × 10^{-8}

* No trace taken. † Addition of benzene caused a measured increase of $2·43 \times 10^{-9}$ mho.

TABLE 3.

Soln.	10^4C	m_b (g.)	$\Delta\kappa_b$	$\Delta\kappa_b$ (%) *	$10^3\Delta\kappa_b/C$	$10^4\Delta\kappa_b/m_b$
6	0·2534	0·238	$6·98 \times 10^{-10}$	0·125	0·276	0·294
5	3·927	0·238	$1·00 \times 10^{-8}$	0·145	0·255	4·21
1	17·13	0·220	$9·64 \times 10^{-8}$	0·270	0·563	43·8
4	30·54	0·238	$7·77 \times 10^{-7}$	1·54	2·54	323
2	64·39	0·356	$1·13 \times 10^{-6}$	0·846	1·75	317
3	280·9	0·238	$2·50 \times 10^{-6}$	0·691	0·890	1050

* $\Delta\kappa_b$ (%) = $\Delta\kappa_b$ expressed as a percentage of κ_1.

silver ions. The large variation in $\Delta\kappa_b/m_b$ however shows that the conductometric effect of the benzene is not continuously dependent on the quantitative composition of the binary solvent mixture.

These facts are therefore not consistent with the formation of stoicheiometric complex

ions as claimed by Taufen, Murray, and Cleveland.[3] It is possible that silver ions, moving through a solution under the influence of an applied potential, tend to drag benzene molecules with them owing to the affinity between the electrophilic ions and the π bonds of the aromatic molecules. Apparently here again the effect should depend in some way on the benzene concentration but in this case it need not be of a linear nature. The " toluene trace " (Fig. 3) supports this. Toluene, when added to a silver nitrate solution, causes an increase in conductivity which is consistent with the effects of organic bases on solutions of this salt [1c] and suggests that it is the aromatic nature of benzene which is responsible for its effect on silver ions. The theory of the formation of loose benzene–silver ion aggregates in solution, although basically different from the theory of stoicheiometric complex-ion formation as suggested by Taufen, Murray, and Cleveland, need not be totally incompatible with their results.

Experimental.—The use of the 1500 c./sec. bridge was described earlier.[1a] Di*cyclo*pentadiene was purified by two distillations and *cyclo*pentadiene was prepared by " cracking " the dimer in a 14 in. glass tube packed with glass helices. Benzene was purified by Rybicka and Wynne-Jones's method.[8] Polystyrene was reprecipitated from carbon tetrachloride with methyl alcohol.

We thank the Central Research Fund of the University of London for a grant (to V. S. G.) and Imperial Chemical Industries Limited for a grant for apparatus.

BATTERSEA COLLEGE OF TECHNOLOGY, LONDON, S.W.11. [*Received, October 10th*, 1957.]

[8] Rybicka and Wynne-Jones, *J.*, 1950, 3671.

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310. *The Unsaturation and Tautomeric Mobility of Heterocyclic Compounds. Part XII.* The Methylation of 6 : 4′-Disubstituted and 4′-Substituted 2-Anilinobenzothiazoles.*

By R. F. HUNTER, E. R. PARKEN, and EILEEN M. SHORT.

The effect of *para*-substituents to the nitrogen atoms of the semicyclic amidine system in 2-anilinobenzothiazoles on the proportion of methyl isomers derived from the tautomeric forms on methylation with methyl iodide alone has been examined. The formation of a strong preponderance of 2-phenyliminobenzothiazoline derivatives which occurs in all cases is attributed, on the basis of the ammonium mechanism of methylation, to the stability of the amino-aromatic form. It is concluded that a *p*-methyl group activates the unshared electrons of the nitrogen atom relative to hydrogen while halogen deactivates them, and the effect of the same substituent is greater when in the benzene ring of the benzothiazole system than in the side-chain benzene ring. In the presence of ethoxide ions there is a profound shift in the direction of methylation towards the production of 2-*N*-methylanilino-isomers, which is interpreted on the basis of operation of an amide mechanism of methylation of the amino-aromatic form, which is probably the main reaction in the presence of excess of sodium ethoxide.

IT was observed earlier [1] that 6-substituted 2-aminobenzothiazoles (I) are methylated exclusively on the nuclear nitrogen atom of the amidine system, irrespective of the nature of the *para*-substituent to this (I; R = Me, OEt, I, Br, Cl, F, or NO_2), yielding 2-imino-3-methylbenzothiazolines (II). This was attributed to the stability of the amino-aromatic form in which the formation of the sextet [2] can be pictured without calling on the unshared

* Part XI, *J.*, 1938, 321.

[1] Hunter and Jones, *J.*, 1930, 2190; Dyson, Hunter, Jones, and Styles, *J. Indian Chem. Soc.*, 1931, 8, 147.

[2] Armit and Robinson, *J.*, 1925, **127**, 1605; Goss and Ingold, *J.*, 1928, 1268.

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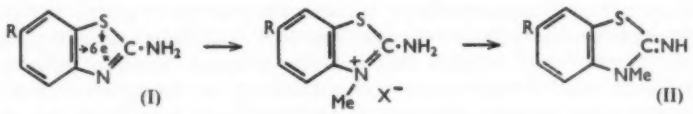
electrons of the nuclear nitrogen atom. The inertness of sulphur of the thiazole ring provides an example of an atom which, while it cannot provide unshared electrons for purposes such as salt formation or addition of bromine, can contribute these to another process such as the formation of the " aromatic " sextet.



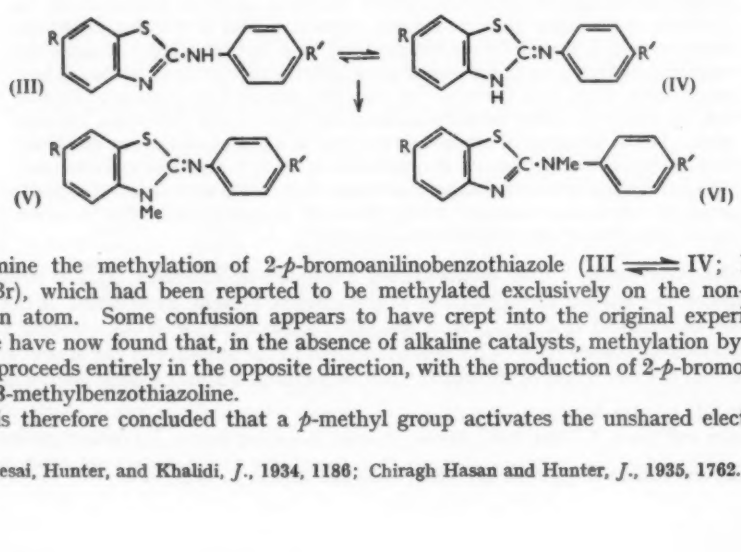
(I) (II)

The conjugating effect of the phenyl group in the anilino-substituent in 2-anilinobenzothiazole (III ⇌ IV; R = R′ = H), however, enables the nitrogen atom to which it is attached to compete with the thiazole-nitrogen atom in methylation, leading to substantial formation of the second methyl isomer (VI; R = R′ = H) and similar results were observed for the oxazole and selenazole analogues.[3] In accordance with this, we have found that 2-*cyclo*hexylaminobenzothiazole reacts apparently wholly in the amino-aromatic form, yielding 2-*cyclo*hexylimino-3-methylbenzothiazoline.

The effect of substituents on the proportion of isomeric methyl derivatives obtained by methylation of 6 : 4′-disubstituted (III ⇌ IV; R = R′) and 4′-substituted 2-anilinobenzothiazoles (III ⇌ IV; R = H) has now been examined.

Methylation of 6-methyl-2-*p*-toluidinobenzothiazole (III ⇌ IV; R = R′ = Me) with methyl iodide contrasted with the original experiment with 2-anilinobenzothiazole in that the proportion of isomer (VI; R = R′ = Me) isolable (as picrate obtained by fractional crystallisation) was only of the order of 3%. 6-Chloro-2-*p*-chloroanilinobenzothiazole (III ⇌ IV; R = R′ = Cl), however, gave a mixture of isomers (V and VI; R = R′ = Cl) (isolated as picrate) in which the former predominated in the ratio of approximately 3 : 1.

2-*p*-Toluidinobenzothiazole (III ⇌ IV; R = H, R = Me) gave a mixture of 2-*p*-tolylimino-3-methyl- and 2-*N*-methyl-*p*-toluidino-isomers in the proportion of approximately 4 : 1 in favour of the former, very close to the result obtained for 2-anilinobenzothiazole itself. 2-*p*-Chloroanilinobenzothiazole (III ⇌ IV; R = H, R′ = Cl) reacted apparently exclusively in the amino-aromatic form, yielding 2-*p*-chlorophenylimino-3-methylbenzothiazoline and no detectable quantity of the isomer. This led us to



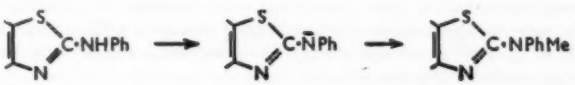
re-examine the methylation of 2-*p*-bromoanilinobenzothiazole (III ⇌ IV; R = H, R′ = Br), which had been reported to be methylated exclusively on the non-nuclear nitrogen atom. Some confusion appears to have crept into the original experiments[1] and we have now found that, in the absence of alkaline catalysts, methylation by methyl iodide proceeds entirely in the opposite direction, with the production of 2-*p*-bromophenylimino-3-methylbenzothiazoline.

It is therefore concluded that a *p*-methyl group activates the unshared electrons of

[3] Desai, Hunter, and Khalidi, *J.*, 1934, 1186; Chiragh Hasan and Hunter, *J.*, 1935, 1762.

the nitrogen atom relative to hydrogen, while halogens deactivate them, and that the effect of the same substituent is greater when in the benzene ring of the benzothiazole system than in the side-chain benzene ring.

The effect of alkoxide ions on the direction of methylation was also examined and in all cases caused a profound shift towards the production of the 2-*N*-methylarylamino-isomer.[4] On treatment in ethanolic sodium ethoxide with methyl sulphate, 6-methyl-2-*p*-toluidinobenzothiazole gave a mixture in which the 2-*N*-methyl-*p*-toluidino-derivative predominated, and 2-*p*-chloroanilinobenzothiazole gave roughly equal proportions of methyl isomers. 6-Chloro-2-*p*-chloroanilinobenzothiazole, which could not be methylated under similar conditions with methyl sulphate, gave with methyl iodide in the presence of ethanolic sodium ethoxide apparently exclusive methylation on the non-nuclear nitrogen atom. These results are interpreted on the basis of the operation of an amide mechanism of methylation of the amino-aromatic form, analogous to that for methylation of 2-hydroxybenzothiazoles in alkaline solution,[5] which is probably the main reaction in the presence of excess of sodium ethoxide:



The 3-methyl-2-phenyliminobenzothiazolines required for identification of methylation products were synthesised by cyclisation of the corresponding *NN'*-diaryl-*N*-methyl(thioureas) with bromine, the methyl group directing cyclisation on to the aromatic nucleus of the nitrogen atom to which it is attached in the intermediate bromothiol derivative through which thiazole cyclisation is presumed to take place.[6] Attempts to prepare 2-arylimino-3-methylbenzothiazolines by heating 2-thio-3-methylbenzothiazoline with arylamines were unsuccessful, as were similar experiments with 3-methylbenzothiazolin-2-one, even in the presence of dehydrating agents such as phosphorus oxychloride.

Experimental

6-Methyl-2-p-toluidinobenzothiazole.—This base was prepared[7] from *NN'*-di-*p*-tolyl(thiourea) and bromine, crystallised from alcohol–ethyl acetate in needles, m. p. 162°. The *picrate*, prepared in acetone, crystallised from ethyl acetate in pale yellow needles, m. p. 252° (Found: S, 6·7. $C_{15}H_{14}N_2S,C_6H_3O_7N_3$ requires S, 6·6%).

Methylation by methyl iodide. The base (5 g.) was heated with methyl iodide in sealed tubes at 100° for the times indicated and the product digested with 30% aqueous potassium hydroxide on a water-bath for 1—2 hr., then extracted with chloroform, and the gummy base stirred with cold absolute ethanol. The colourless residue was collected and the recovered uncrystallisable gum was treated in acetone with the calculated amount of picric acid. The picrate was fractionally recrystallised from ethyl acetate. Fractions of similar m. p. were united and recrystallised after mixed m. p. determinations. The final picrate fractions were very gummy and yielded sufficient solid for m. p. determinations only with difficulty. Results are tabulated.

MeI (ml.)	Time (hr.)	Residue, m. p. 118° (g.)	Gum (g.)	Yield (g.) (and m. p.) of picrate fractions I	II	III (gum)
7·5	1	3·4	2	0·56 (242°)	1·5 (162°)	1
7·5	2·5	3·7	1·9	0·07 (242°)	1·65 (144°)	0·6
15	2·5	3·87	1·35	0·05 (240°)	1·2 (146°)	0·6
7·5	4·5	3·84	1·57	0·05 (240°)	1·4 (145°)	0·5
15	4·5	3·8	1·38	0·06 (240°)	1·42 (147°)	0·6

[4] Hunter and Wali, *J.*, 1937, 1513.
[5] Hunter and Parken, *J.*, 1935, 1755.
[6] Hunter, *Sir P. C. Ray Commemoration Vol., J. Indian Chem. Soc.*, 1933, p. 73.
[7] Hunter, *J.*, 1925, **127**, 2023.

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The picrate fractions of m. p. 240—242°, on recrystallisation, had m. p. 250—251° alone and when mixed with 6-methyl-2-*p*-toluidinobenzothiazole picrate. The residues of m. p. 118° consisted of 3 : 6-*dimethyl*-2-p-*tolyliminobenzothiazoline*, which on recrystallisation formed needles, m. p. 121° (Found: C, 71·8; H, 6·0; N, 10·3; S, 11·8. $C_{16}H_{16}N_2S$ requires C, 71·6; H, 6·0; N, 10·4; S, 11·8%). Its *picrate* formed needles (from ethyl acetate), m. p. 175—176° (Found: S, 6·5. $C_{16}H_{16}N_2S,C_6H_3O_7N_3$ requires S, 6·4%). The picrate of m. p. 162° obtained in the first experiment gave solely the picrate of m. p. 176° on recrystallisation. Fractional crystallisation of the picrates of m. p. 144—147° from ethyl acetate furnished mainly the 3 : 6-dimethyl-2-*p*-tolyliminobenzothiazoline picrate, m. p. 176°, accompanied by small amounts of 6-methyl-2-*N*-methyl-*p*-toluidinobenzothiazole picrate, m. p. 165°, the united yield of which from the four experiments was 0·8 g.

Methylation by dimethyl sulphate in ethanolic sodium ethoxide. The base (2 g.) in ethanolic sodium ethoxide (prepared from 1 g. of sodium in 100 ml. of ethanol) was heated with dimethyl sulphate (6 ml.) under reflux for 4 hr., treated with excess of ammonia (*d* 0·880) after removal of the bulk of the alcohol, and extracted with chloroform. An alcoholic solution of the resulting gum deposited 3 : 6-dimethyl-2-*p*-tolyliminobenzthiazoline (0·35 g.), m. p. 121° alone and when mixed with the previous specimen, after recrystallisation (Found: S, 11·8%). The recovered gum was separated by light petroleum into a residue of unmethylated base (0·7 g.; m. p. 162°) and a gum (0·6 g.) which in acetone gave a picrate which on recrystallisation from ethyl acetate had m. p. 165° alone and m. p. 165—166° when mixed with authentic 6-methyl-2-*N*-methyl-*p*-toluidinobenzothiazole picrate.

Synthesis of 6-methyl-2-N-*methyl*-p-*toluidinobenzothiazole and* 3 : 6-*dimethyl*-2-p-*tolyliminobenzothiazoline.* (i) 2-Chloro-6-methylbenzothiazole (1·5 g.) and *N*-methyl-*p*-toluidine (1 g.) were heated until a vigorous reaction occurred. The basified product extracted with chloroform did not crystallise and was converted into the *picrate* of 6-methyl-2-*N*-methyl-*p*-toluidinobenzothiazole which after several recrystallisations from ethyl acetate formed yellow needles, m. p. 166° (Found: C, 53·15; H, 3·8; S, 6·5. $C_{16}H_{16}N_2S,C_6H_3O_7N_3$ requires C, 53·1; H, 3·8; S, 6·4%). (ii) N-*Methyl*-NN'-*di*-p-*tolyl*(*thiourea*), prepared from *p*-tolylthiocarbimide (3 g.) and *N*-methyl-*p*-toluidine (2·4 g.) in ethanol, formed needles, m. p. 103° (Found: S, 11·8. $C_{16}H_{18}N_2S$ requires S, 11·85%). A solution of the thiourea (2 g.) in chloroform (20 ml.) was heated with bromine (2 ml. in 2 ml. of chloroform) under reflux for 20 min. and the orange-red hydroperbromide obtained by concentration at laboratory temperature under reduced pressure was ground with aqueous sulphurous acid until colourless. The basified product on recrystallisation from ethanol had m. p. 110—116° but gave 3 : 6-dimethyl-2-*p*-tolyliminobenzothiazoline picrate, m. p. 176° alone and when mixed with a specimen obtained by methylation of 6-methyl-2-*p*-toluidinobenzothiazole (Found: S, 6·5%).

6-*Chloro*-2-p-*chloroanilinobenzothiazole*.[8]—This base, m. p. 224°, gave a *picrate* as needles (from ethyl acetate), m. p. 258° (Found: S, 6·3. $C_{13}H_8N_2Cl_2S,C_6H_3O_7N_3$ requires S, 6·1%).

The base (10 g.) and methyl iodide (10 ml.) were heated at 100° for 9—10 hr., and the product digested with hot 30% aqueous potassium hydroxide for several hours to ensure complete decomposition of hydriodides. The alcoholic solution of the gum isolated by chloroform deposited 6-chloro-2-*p*-chlorophenylimino-3-methylbenzothiazoline which after recrystallisation from methanol–ethyl acetate formed needles (3·3 g.), m. p. 119°, and m. p. 120° when mixed with a specimen synthesised from *NN'*-di-*p*-chlorophenyl-*N*-methyl(thiourea), and gave a *picrate*, needles, m. p. 158—159° (Found: Cl, 13·1. $C_{14}H_{10}N_2Cl_2S,C_6H_3O_7N_3$ requires Cl, 13·2%). Fractional crystallisation of the picrate from the gum obtained from the mother-liquors gave 0·8 g. of 6-chloro-2-*p*-chloroanilinobenzothiazole picrate (m. p. 259° and 251°), and 1·9 g. of 6-chloro-2-*p*-chloro-*N*-methylanilinobenzothiazole picrate (needles, m. p. 167—169°).

Attempted methylation of 6-chloro-2-*p*-chloroanilinobenzothiazole in ethanolic sodium ethoxide as in the previous case, but with a higher concentration of dimethyl sulphate, proved unsuccessful. A mixture of the base (2 g.), ethanolic sodium ethoxide (sodium, 0·5 g.; ethanol, 4 ml.), and methyl iodide (4 ml.) was heated in a sealed tube at 100° for 5—6 hr. The basified product gave 6-chloro-2-*p*-chloro-*N*-methylanilinobenzothiazole, which had m. p. 96° after recrystallisation and gave a picrate, m. p. 169°. The mother-liquors gave a further 0·9 g. of this base and the residual gum (0·4 g.) furnished its picrate. No evidence was obtained of the presence of 6-chloro-2-*p*-chlorophenylimino-3-methylbenzothiazoline.

[8] Dyson, Hunter, and Soyka, *J.*, 1929, 458.

6-*Chloro*-2-p-*chloro*-N-*methylanilinobenzothiazole*, obtained by condensation of 2 : 6-dichlorobenzothiazole and *p*-chloro-*N*-methylaniline, formed needles (from alcohol), m. p. 95° (Found: Cl, 22·75; S, 10·2. $C_{14}H_{10}N_2Cl_2S$ requires Cl, 23·0; S, 10·4%). The picrate formed deep yellow needles (from ethyl acetate), m. p. 169—170° (Found: C, 44·4; H, 2·4; Cl, 13·1; S, 5·9. Calc. for $C_{14}H_{10}N_2Cl_2S,C_6H_3O_7N_3$: Cl, 44·4; H, 2·5; Cl, 13·1; S, 5·9%).

NN'-*Di*-p-*chlorophenyl*-N-*methyl*(*thiourea*) formed needles (from ethanol), m. p. 148° (Found: Cl, 22·9; S, 10·2. $C_{14}H_{12}N_2Cl_2S$ requires Cl, 22·8; S, 10·3%). 6-*Chloro*-2-p-*chlorophenylimino*-3-*methylbenzothiazoline*, prepared from this thiourea, formed needles (from alcohol), m. p. 121° (Found: C, 54·5; H, 3·6; N, 8·8; Cl, 22·8; S, 10·4. $C_{14}H_{10}N_2Cl_2S$ requires C, 54·4; H, 3·2; N, 9·1; Cl, 23·0; S, 10·6%), and gave a picrate, m. p. 158° (Found: Cl, 13·1%).

2-p-*Toluidinobenzothiazole*.—The alcoholic solution of the gum obtained by methylation of the base (5·4 g.) with methyl iodide (10 ml.) at 100° for 3—4 hr. deposited 3-*methyl*-2-p-*toluidinobenzothiazoline* (2 g.), m. p. 87°, and the recovered gum (2·6 g.) gave a further 1 g. (m. p. 88°) on washing with cold acetone; this had m. p. 89° after recrystallisation (Found: S, 12·3. $C_{15}H_{14}N_2S$ requires S, 12·6%). Fractional crystallisation of the picrate from the gum recovered from the acetone solution gave 3-*methyl*-2-p-*tolyliminobenzothiazoline picrate*, m. p. 180° alone and when mixed with an authentic specimen (Found: S, 6·45. $C_{15}H_{14}N_2S,C_6H_3O_7N_3$ requires S, 6·6%), a further fraction, m. p. 176° (total 0·6 g.), and impure 2-*N*-methyl-*p*-toluidinobenzothiazole picrate, m. p. 144° and 146°; total: 1·4 g.) which after recrystallisation had m. p. 170° alone, and 169—170° when mixed with a authentic specimen.

2-*N*-Methyl-*p*-toluidinobenzothiazole, obtained as a gum from 2-chlorobenzothiazole and *N*-methyl-*p*-toluidine, gave a *picrate* which formed deep yellow needles (from ethyl acetate), m. p. 170° (Found: C, 52·3; H, 3·8; N, 14·2; S, 6·4. $C_{15}H_{14}N_2S,C_6H_3O_7N_3$ requires C, 52·2; H, 3·5; N, 14·45; S, 6·6%).

N-*Methyl*-N-*phenyl*-N'-p-*tolyl*(*thiourea*) formed needles (from alcohol), m. p. 126° (Found: S, 12·7. $C_{15}H_{16}N_2S$ requires S, 12·8%). 3-Methyl-2-*p*-tolyliminobenzothiazoline, obtained by cyclization of the thiourea with bromine, was a gum and was converted into the *picrate* which formed needles (from alcohol), m. p. 180° (Found: C, 52·2; H, 3·7; N, 14·2; S, 6·4%).

2-p-*Chloroanilinobenzothiazole*.—The *picrate* formed needles, m. p. 239° (Found: S, 6·4. $C_{13}H_9N_2ClS,C_6H_3O_7N_3$ requires S, 6·5%). (i) The ethanolic solution of basified product from methylation of this base (10 g.) with methyl iodide (15 ml.) at 100° for 6 hr. gave 5 g. of 2-p-*chlorophenylimino*-3-*methylbenzothiazoline*, m. p. 105° (108°) which rose to 109° on recrystallisation (Found: S, 11·55. $C_{14}H_{11}N_2ClS$ requires S, 11·6%), and gave a picrate which had m. p. 180° alone and when mixed with an authentic specimen. A further 2 g. of this methyl derivative were obtained from mother-liquors, and the residual gum (0·8 g.) gave the picrate of this [m. p. 179° (177°)] and of unchanged base (m. p. 235°). (ii) The picrate of the gum obtained by methylation of the base (5 g.) in ethanolic sodium ethoxide with dimethyl sulphate (15 ml.) for 4 hr. gave the picrate (1 g.; m. p. 233°) of unchanged base, and impure 2-*p*-chlorophenylimino-3-methylbenzothiazoline (m. p. 176—177°, 172—173° total: 1 g.; and 0·8 g. of m. p. 163—170°). The mother-liquors gave an obvious mixture of crystals which were collected separately and on recrystallisation gave the picrate (0·65 g.; m. p. 173—174°) of the 2-phenylimino-3-methyl derivative, and 2-p-*chloro*-N-*methylanilinobenzothiazole picrate*, m. p. 162—163° (1·75 g.) (Found: S, 6·2. $C_{14}H_{11}N_2ClS,C_6H_3O_7N_3$ requires S, 6·4%). The mother-liquors gave a further 1·1 g. of the latter, m. p. 153—159°.

2-p-*Chloro*-N-*methylanilinobenzothiazole*, prepared from 2-chlorobenzothiazole, formed a gum which crystallised from ethanol, then having m. p. 103—104° (Found: S, 11·4. $C_{14}H_{11}N_2ClS$ requires S, 11·65%), and gave a picrate, m. p. 162° (Found: C, 47·9; H, 3·1; S, 6·2. Calc. for $C_{14}H_{11}N_2ClS,C_6H_3O_7N_3$: C, 47·4; H, 2·8; S, 6·4%).

N'-p-*Chlorophenyl*-N-*methyl*-N-*phenyl*(*thiourea*) formed plates, m. p. 131—132° (Found: Cl, 12·6; S, 11·5. $C_{14}H_{13}N_2ClS$ requires Cl, 12·8; S, 11·6%). 2-*p*-Chlorophenylimino-3-methylbenzothiazoline, obtained by cyclisation of this with bromine, formed needles (from ethanol), m. p. 110° (Found: C, 61·3; H, 4·0; N, 9·9; Cl, 12·7; S, 11·5. Calc. for $C_{14}H_{11}N_2ClS$: C, 61·2; H, 4·0; N, 9·9; Cl, 12·9; S, 11·65%), whose *picrate* formed needles, m. p. 182° (Found: S, 6·1%). This base was also prepared by heating 2-imino-3-methylbenzothiazoline (1·6 g.) and *p*-chloroaniline (1·9 g.) at 220—230° for 3½ hr., then having m. p. and mixed m. p. 108—109° (picrate, m. p. and mixed m. p. 180°).

2-p-*Bromoanilinobenzothiazole*.—The picrate of the base formed needles (from ethyl acetate), m. p. 243° (Found: S, 6·0. $C_{13}H_9N_2BrS,C_6H_3O_7N_3$ requires S, 6·0%). (i) Crystallisation of

the basified product obtained by treating the base (10 g.) with methyl iodide (15 ml.) at 100° for 8—10 hr. gave (from alcohol) 2-p-*bromophenylimino*-3-*methylbenzothiazoline* (7·3 g.), needles, m. p. 105° undepressed on admixture with an authentic specimen (Found: S, 9·95. $C_{14}H_{11}N_2BrS$ requires S, 10·0%). The gummy residue gave a further 1·2 g. (m. p. 103—105°) when washed with cold acetone, and the extract furnished 2-*p*-bromoanilinobenzothiazole picrate, m. p. 237°, accompanied by 2-p-*bromophenylimino*-3-*methylbenzothiazoline picrate*, m. p. 184° (Found: S, 5·8. $C_{14}H_{11}N_2BrS,C_6H_3O_7N_3$ requires S, 5·8%). (ii) The gum obtained by methylation of the base (4 g.) in ethanolic sodium ethoxide with dimethyl sulphate (16 ml.) gave on treatment with cold ethanol 1·8 g. of 2-*p*-bromo-*N*-methylanilinobenzothiazole, m. p. 117—118°, and microcrystalline fractions which yielded 2-*p*-bromophenylimino-3-methylbenzothiazoline picrate (2·9 g.) and the picrate (0·8 g.) of the isomer. From the uncrystallisable gum a further 0·1 g. and 0·25 g. respectively of these picrates were isolated, with 0·2 g. of the picrate of unchanged base. 2-p-*Bromo*-N-*methylanilinobenzothiazole*, prepared from 2-chlorobenzothiazole and *p*-bromo-*N*-methylaniline, had m. p. 115—116° (Found: C, 52·7; H, 3·5; Br, 24·8; S, 10·1. $C_{14}H_{11}N_2BrS$ requires C, 52·7; H, 3·4; Br, 25·1; S, 10·0%). The *picrate* obtained from this had m. p. 166° (Found: S, 5·9%). N′-p-*Bromophenyl*-N-*methyl*-N-*phenyl*(*thiourea*) formed plates, m. p. 147° (Found: Br, 25·1; S, 10·0. $C_{14}H_{13}N_2BrS$ requires Br, 24·9; S, 10·0%). 2-*p*-Bromophenylimino-3-methylbenzothiazoline, obtained by cyclisation with bromine, formed needles, m. p. 105° (Found: C, 52·7; H, 3·5; N, 8·4; Br, 24·9; S, 9·95%). The picrate from this had m. p. 184° (Found: S, 5·9%).

Methylation of 2-*Anilinobenzothiazole*.—(i) This base (4 g.) with methyl iodide (6 ml.) at 100° for 6—7 hr. gave 3-methyl-2-phenyliminobenzothiazoline (3 g.), m. p. 96° (after recrystallisation, undepressed by a specimen prepared from 2-imino-3-methylbenzothiazoline and aniline), and gum which yielded 0·5 g. of the picrate of this (m. p. 162°) and 1·1 g. of 2-*N*-methylanilinobenzothiazole picrate, m. p. 184° (after recrystallisation, undepressed by an authentic specimen). (ii) Methylation of the base (2 g.) in ethanolic sodium ethoxide with dimethyl sulphate (12 ml.) gave 2-*N*-methylanilinobenzothiazole picrate (2·7 g.) and the picrate (1·15 g.) of the isomer.

2-cyclo*Hexylaminobenzothiazole*.—The *base*, prepared from *N*-*cyclo*hexyl-*N*′-phenyl(thiourea) (m. p. 145—146°) and crystallised from methanol, had m. p. 103—104° (Found: C, 67·4; H, 6·7; N, 11·9; S, 13·7. $C_{13}H_{16}N_2S$ requires C, 67·2; H, 6·9; N, 12·1; S, 13·8%). The *picrate* formed needles (from ethyl acetate), m. p. 233—234° (Found: S, 7·1. $C_{13}H_{16}N_2S,C_6H_3O_7N_3$ requires S, 6·9%). The gum obtained by methylation of this base (2 g.) with methyl iodide (3 ml.) at 100° for 18 hr. gave solely 2-cyclo*hexylimino*-3-*methylbenzothiazoline picrate*, m. p. 145° (after recrystallisation) undepressed on admixture with a specimen obtained from the base prepared by heating 2-imino-3-methylbenzothiazoline and *cyclo*hexylamine at 185—190° (Found: C, 50·8; H, 4·5; S, 6·4. $C_{14}H_{16}N_2S,C_6H_3O_7N_3$ requires C, 50·5; H, 4·4; S, 6·7%).

One of the authors is greatly indebted to Professor Sir Christopher Ingold, F.R.S., for helpful discussions.

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[*Received, October 26th,* 1956.]

311. *Substitution Reactions in the Trisethylenediaminecobalt*(III) *Ion.*

By J. A. Friend and E. K. Nunn.

The hydrolysis of the trisethylenediaminecobalt(III) ion is studied at relatively high alkali concentrations and high temperatures. The ion is stable at low temperatures and low alkali concentrations in the absence of catalysts. The rate is followed spectrophotometrically at temperatures from 70° to 90° c.

Although each run gives a first-order plot, the overall reaction has second-order kinetics. The effect of increasing the ionic strength of the reaction mixture with sodium nitrate is investigated; no appreciable salt effect is observed, probably owing to the high ionic strength of the mixtures.

The activation energy for $[Co\ en_3]^{3+} \longrightarrow [Co\ en_2(OH)_2]^+$, which involves the rupture of two bonds, is 38 kcal. mole^{-1} for concentrations of hydroxyl ion greater than 0·1N. Below this the dependence of rate on concentration of hydroxyl-ion changes and the activation energy appears to become smaller. Possible mechanisms for the reaction are discussed.

Recent studies of substitution reactions in octahedral complexes of tervalent cobalt have been due mainly to Bailar,[1] Ingold and Nyholm,[2] and Basolo [3] and their collaborators. Much has appeared more recently, dealing mostly with reactions of ions of the general formula $[Co\ en_2X_2]^+$.[4,5] We have begun to investigate the more stable trisethylenediamine ion. The first experiments used the trisethylenediaminechromium(III) ion, but even at as low as 50° the complex ion decomposed in solution too rapidly to allow the study of any reaction with other ions (such as chloride). At 35° no reaction could be observed, although Schläfer and Kling [6] found a slow transformation of $[Cr\ en_3]^{3+}$ into $[Cr\ en_2(H_2O)_2]^{3+}$ in solution at room temperature during some weeks.

Attention was therefore directed to the trisethylenediaminecobalt(III) ion, which is more stable. We tried to study the substitution of ethylenediamine by chloride ion, but this did not occur even in aqueous solution at 100°. Reaction with hydroxyl ion did, however, occur at measurable rates in aqueous solution above 70°. Taube [7] has stated (apparently on Jørgensen's authority) that $[Co\ en_3]^{3+}$ is unaffected by boiling alkali, but this does not appear to be so, although it does not completely decompose to the oxide.[8] Bjerrum and Rasmussen [9] studied the reaction

$$[Co\ en_3]^{3+} + 2OH^- \rightleftharpoons [Co\ en_2(OH)_2]^+ + en$$

in aqueous solution, in the presence of charcoal as a catalyst, at 25°. The product contained approximately equal amounts of the *cis*- and the *trans*-isomer. We used a large excess of alkali, but no charcoal, so as to lead to hydroxylation rather than to aquation.

[1] (*a*) Bailar and Auten, *J. Amer. Chem. Soc.*, 1934, **56**, 774; (*b*) Bailar, Haslam, and Jones, *ibid.*, 1936, **58**, 2226.
[2] (*a*) Brown, Ingold, and Nyholm, *J.*, 1953, 2674; (*b*) Brown and Ingold, *ibid.*, p. 2680; (*c*) Brown and Nyholm, *ibid.*, p. 2696.
[3] (*a*) Basolo, Bergmann, and Pearson, *J. Phys. Chem.*, 1952, **56**, 22; (*b*) Pearson, Boston, and Basolo, *J. Amer. Chem. Soc.*, 1952, **74**, 2943.
[4] Basolo, *Chem. Rev.*, 1953, **52**, 459.
[5] Basolo, Stone, and Pearson, *J. Amer. Chem. Soc.*, 1953, **75**, 819.
[6] Schläfer and Kling, *Z. anorg. Chem.*, 1956, **287**, 296.
[7] Taube, *Chem. Rev.*, 1952, **50**, 69.
[8] Brigando, *Compt. rend.*, 1953, **236**, 708.
[9] Bjerrum, J., and Rasmussen, *Acta Chem. Scand.*, 1952, **6**, 1265.

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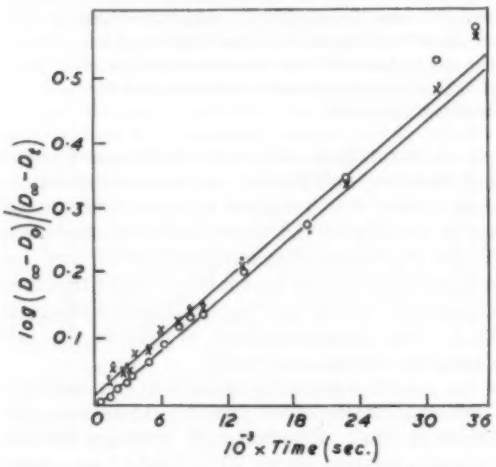
Experimental

Trisethylenediaminecobalt(III) chloride was prepared according to the method of " Inorganic Syntheses." [10] It was analysed for cobalt by the pyridine–thiocyanate method after being evaporated with concentrated sulphuric acid, and for chloride by titration with silver nitrate [Found: Co, 15·9, 15·1; Cl, 28·3, 28·5, 28·5. Calc. for $Co(C_2H_8N_2)_2Cl_3,1{\cdot}5H_2O$: Co, 15·8; Cl, 28·6%]. The standardised sodium hydroxide solutions used were carbonate-free.

Absorption spectra were measured on a Unicam S.P. 500 spectrophotometer. The reaction was followed by reading optical density at 560 mμ, where the absorption of $[Co\ en_3]^{3+}$ is negligible; at 510 mμ, where the absorption is still low, and *cis*- and *trans*-$[Co\ en_2(OH)_2]^+$ both have maxima; and at 460 mμ, where $[Co\ en_3]^{3+}$ has a maximum and the curves for the two dihydroxo-compounds cross. One set of readings was taken at 494 mμ, where $[Co\ en_3]^{3+}$ and $[Co\ en_2(OH)_2]^+$ have the same extinction coefficient. This showed that the total cobalt concentration in the solution was not changing through evaporation.

Experiments were carried out in stoppered 250 ml. " Pyrex " flasks. The solutions used were approximately 2·8mM in $[Co\ en_3]^{3+}$. Weighed amounts of the salt were placed in 250 ml.



Reaction of $[Co\ en_3]Cl_3$ *with 0·5N-sodium hydroxide at 70°.*
○ Readings at 560 mμ.
× Readings at 510 mμ.
$k = 3{\cdot}32 \times 10^{-5}$ sec.$^{-1}$.

volumetric flasks and sodium hydroxide solution was added to make 250 ml. The standard solutions were then transferred to the reaction flasks in the thermostat, and about 3 min. allowed for the mixture to reach equilibrium before readings were taken. Samples were withdrawn at intervals and chilled in an ice-bath before the optical density was measured.

Results.—The reactions followed a first-order course with respect to alkali concentration. A typical run is shown in Fig. 1, which also shows that the slopes derived from readings at

Table 1. *Values of rate constant for constant sodium hydroxide concentration* (0·5N) *at different temperatures.*

Temp. (° c)	70·0	75·2	80·0	91·0
10^5k (sec.$^{-1}$)	3·32	8·53	20·0	85·0

Table 2. *Variation of rate constants with sodium hydroxide concentration at* 80°.

[NaOH] (N)	0·05	0·10	0·20	0·50	0·664	1·0
10^4k (sec.$^{-1}$)	1·28	1·54	1·65	2·00	2·17	2·65

510 mμ and 560 mμ agree well. There is some deviation from linearity in the later stages. In Table 1 the variation of rate constant with temperature is shown; the activation energy is about 38 kcal. mole^{-1}.

[10] Work, " Inorganic Syntheses," McGraw-Hill Book Company, Inc., New York, 1946, Vol. II, p. 221.

In Table 2 are listed the values of k found at constant temperature (80°) and ammine concentration, for different concentrations of sodium hydroxide. A plot of these data shows that the dependence of the rate constant on sodium hydroxide concentration is linear down to 0·1N, although the point corresponding to 0·05N-NaOH is much lower than the straight line which joins the values of k found at higher concentrations. In 0·01N-NaOH there was little or no reaction after about a week.

It was not possible to detect a change in the rate of reaction on increasing the concentration of ammine, no doubt owing to the large excess of alkali present.

The effect of ionic strength on the reaction rate was studied by adding sodium nitrate to the reaction mixture: results for 80° are in Table 3.

TABLE 3. *Variation of rate constant with ionic strength at* 80° C.

$[NaNO_3]$ (M)	0	0·1	0·2	0·3	0·4
10^5k (0·1N-NaOH)	15·4	10·7	8·68	—	5·57
10^5k (0·5N-NaOH)	20·0	19·2	22·2	17·3	—

TABLE 4. *Variation of rate constant with concentration of sodium hydroxide at constant ionic strength at* 80° C.

$[NaNO_3]$(M)	0	0·2	0·4
[NaOH](N)	0·5	0·3	0·1
10^5k (sec.$^{-1}$)	20·0	14·75	5·57

The graph of log k as a function of (ionic strength)$^{\frac{1}{2}}$ is, for 0·1N-NaOH, linear with a slope of $-1·14$, about one-third of the theoretical value for a reaction between a univalent and a tervalent ion. In 0·5N-NaOH, there is no appreciable salt effect.

These results agree with those of Ašperger and Ingold,[11] who found no salt effect in their experiments on the reaction of sodium hydroxide with the *trans*-(chloronitrobisethylenediamine)-cobalt(III) ion, no doubt owing to their working at the high ionic strength necessary to secure a measurable rate of reaction. When the ionic strength was kept constant at 0·5 and the ratio of sodium hydroxide to sodium nitrate varied, rate constants proportional to the concentration of sodium hydroxide were obtained, thus confirming the overall second-order kinetics of the reaction.

DISCUSSION

The experimental data at a concentration of sodium hydroxide of 0·5N satisfy an equation of the form $k_2 = 6·5 \times 10^{19} \exp(-38{,}000/RT)$. This means that the energy of activation has the unusually high value of about 38 kcal. mole^{-1}, in contrast with the much lower values of 20—30 kcal. found by Ingold, Nyholm, and their collaborators[11,12,13] for most substitution reactions in $[Co\ en_2Cl_2]^+$, $[Co\ en_2(NCS)X]^+$, and $[Co\ en_2NH_3X]^{2+}$, including the bimolecular reaction with hydroxyl ion. At lower concentrations of sodium hydroxide, the reaction mechanism changes, and an activation energy of 32 kcal. mole^{-1} was found for a solution 0·05N in sodium hydroxide. These high activation energies seem to be an expression of the great stability of the $[Co\ en_3]^{3+}$ ion, even as compared with the $[Co(NH_3)_6]^{3+}$ ion. This stability has often been noticed, and is possibly due to steric effects.

Substitution of $[Co\ en_3]^{3+}$ by hydroxyl ion necessarily involves the introduction of two substituents, and takes place apparently in two stages, one of which is bimolecular and rate-controlling. The kinetic expression for the variation of rate constant with temperature in 0·5N-sodium hydroxide indicates that the frequency factor is approximately 10^{20}, even higher than the value of 10^{17} found by Brønsted and Livingstone[14] for the reaction of hydroxyl ion with the chloropentamminocobalt(III) ion. Ašperger and Ingold found a "normal" frequency factor of 10^{11}—10^{12} in the bimolecular substitution of $[Co\ en_2Cl_2]^+$

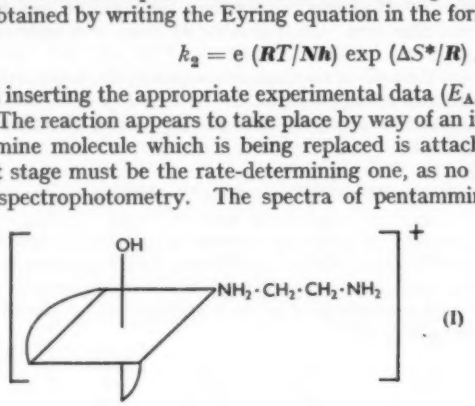
[11] Ašperger and Ingold, *J.*, 1956, 2862.
[12] Ingold, Nyholm, and Tobe, *J.*, 1956, 1691.
[13] Nyholm and Tobe, *J.*, 1956, 1707.
[14] Brønsted and Livingstone, *J. Amer. Chem. Soc.*, 1927, **49**, 435.

by OH^-. In the language of the transition-state theory, the present results can be said to imply an entropy of activation of approximately 30 cal. (mole deg.)$^{-1}$ in accordance with the value to be expected for a reaction involving ions of charges +3 and −1. This result is obtained by writing the Eyring equation in the form

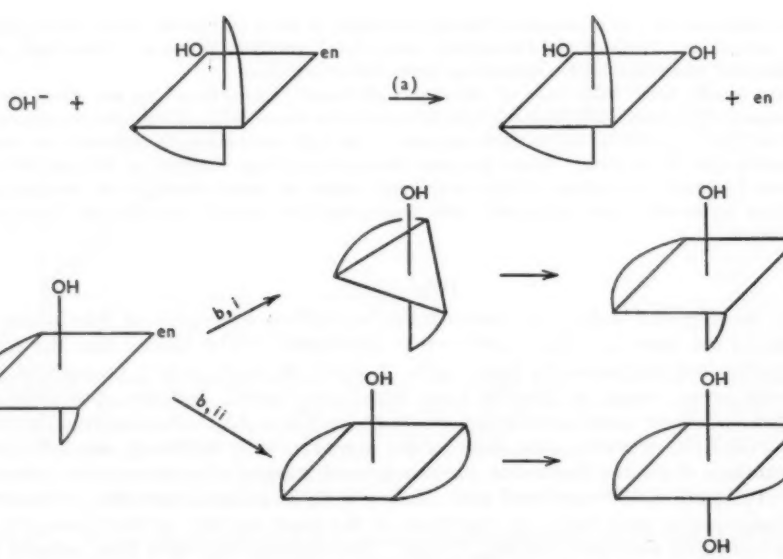
$$k_2 = e\,(RT/Nh)\exp(\Delta S^*/R)\,.\exp(-E_A/RT)$$

and inserting the appropriate experimental data (E_A is the Arrhenius activation energy).

The reaction appears to take place by way of an intermediate ion in which the ethylenediamine molecule which is being replaced is attached at one end only, as in (I). This first stage must be the rate-determining one, as no trace of an intermediate was detected by spectrophotometry. The spectra of pentammines are quite different from those of



(I)



tetrammines, so that if the course of the reaction had involved a rapid formation of an intermediate which then decomposed rapidly, this should have been detectable. It seems reasonable to postulate an intermediate ion of the structure suggested; there are in fact stable co-ordination compounds in which ethylenediamine functions as a unidentate group (see, for example, Drew,[15] Job,[16] and Bjerrum[17]). In the present instance, the adjacent OH group is no doubt responsible for the instability of the second Co–N bond. It has been suggested, particularly by Pearson, Meeker, and Basolo,[18] that the

[15] Drew, *J.*, 1932, 2328.
[16] Job, *Ann. Chim.* (*France*), 1928, **9**, 166.
[17] Bjerrum, J., "Metal Ammine Formation in Aqueous Solution," P. Haase and Sons, Copenhagen, 1941, p. 92.
[18] Pearson, Meeker, and Basolo, *J. Inorg. Nuclear Chem.*, 1955, **1**, 342.

substitutions involving the hydroxyl ion proceed *via* the conjugate base of the cobalt-ammine (mechanism S_N1CB rather than S_N2). This point has been discussed by Ašperger and Ingold,[11] who adhere to the S_N2 mechanism. A firm decision on the question in respect of the ion under discussion would require further work which it has not so far been possible to carry out. Evidence that analogous reactions are in fact S_N2, however, seems adequate. The intermediate could then, either by an edge-displacement giving, with another OH^- ion, $[Co\ en_2(OH)_2]^+$ [path (a)], or by a first-order heterolysis [path (b)], yield the final equilibrium mixture of isomers. The equilibrium between the *cis*- and the *trans*-form is attained so rapidly at the experimental temperatures that the two mechanisms could not be distinguished on this basis. Possibly the former is the more likely mechanism, although the change in configuration in path (b), second stage, could be facilitated by the "*trans*-effect."[19,20]

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[*Received, October 21st,* 1957.]

[19] Quagliano and Schubert, *Chem. Rev.*, 1952, **50**, 201.
[20] Chatt, Duncan, and Venanzi, *Rec. Trav. chim.*, 1956, **75**, 681.

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312. *Urea and Related Compounds. Part V.* Some Sulphenylthioureas.*

By FREDERICK KURZER and W. TERTIUK.

S-Alkyl-*N*-arylsulphenyl- and *S*-alkyl-*NN'*-diarylsulphenyl-*iso*thioureas are obtained in fair yields by the interaction of *iso*thioureas and appropriate quantities of a sulphenyl chloride.

PREVIOUS Parts[1] of this series have dealt with the synthesis and properties of sulphenylureas. We now describe the results of parallel experiments with thioureas.

In general, the sulphenylthioureas were more difficult to prepare and more labile than the urea analogues. Of several reactions[1] that afford sulphenylureas, only one proved suitable in the thiourea series. Interaction of an *iso*thiourea (I; R = Me, CH_2Ph) with appropriate quantities of *o*-nitrobenzenesulphenyl chloride in the presence of alkali in water–acetone gave, as main products, *S*-alkyl-*N*-arylsulphenyl- (II; R = Me, CH_2Ph; R′ = *o*-$NO_2{\cdot}C_6H_4$) or *S*-alkyl-*NN'*-diarylsulphenyl-*iso*thioureas (III; R = Me, CH_2Ph; R′ = *o*-$NO_2{\cdot}C_6H_4$). The former were converted into the latter by more sulphenyl halide.

$$\underset{\text{(I)}}{NH_2{\cdot}C(SR){:}NH} \xrightarrow{R'SCl} \underset{\text{(II)}}{R'S{\cdot}NH{\cdot}C(SR){:}NH} \xrightarrow{R'SCl} \underset{\text{(III)}}{R'S{\cdot}NH{\cdot}C(SR){:}N{\cdot}SR'}$$

The success of these condensations depended on careful control to reduce side reactions resulting in rapid loss of sulphenyl chloride as disulphide (R′S·SR′) or thiolsulphonate (R′SO_2·SR′) (cf. Experimental). The assigned structures of products (II) and (III) are based on composition, molecular weights, and mode of formation and reasoning previously detailed[1] in respect of analogous sulphenyl*iso*ureas. The identity of the substituted *iso*thioureas (II, III) and *iso*ureas (IV, V) is further reflected in their remarkably brilliant colours: monosulphenyl derivatives were scarlet, and disulphenyl derivatives (R′ = *o*-$NO_2{\cdot}C_6H_4$) orange-red in both series.

(IV) R′S·NH·C(OR):NH R′S·NH·C(OR):N·SR′ (V)

Sulphenyl*iso*thioureas (II, III), though stable as solids, were considerably more labile than the corresponding ureas; they were rapidly hydrolysed by acids and alkalis, and

* Part IV, *J.*, 1957, 4461.
[1] Kurzer, *J.*, 1953, 549, 3360.

deposited diaryl disulphide (R'S·SR') slowly even from solutions in non-polar solvents. Dealkylation, which is readily accomplished with sulphenyl*iso*ureas [1] (IV, V), failed with the sulphur analogues: both mono- and di-sulphenyl*iso*thioureas (II, III) were rapidly converted into diaryl disulphide under the most restrained conditions, by Fairfull, Low, and Peak's general method.[2] It is evident that the replacement of the oxygen by the sulphur atom considerably weakens the link between sulphur and nitrogen in the resulting sulphenyl compounds (II, III). This may also explain our inability to synthesise sulphenylthioureas by methods (cf. Experimental) that had previously been found suitable [1] in the preparation of sulphenylureas.

Experimental

S-*Methyl*-N-o-*nitrobenzenesulphenyl*isothiourea.—A solution of *S*-methyl*iso*thiuronium sulphate (5·56 g., 0·04 mole) in water (20 ml.) was diluted with acetone (120 ml.). The resulting precipitate dissolved on addition of 3N-sodium hydroxide (6·7 ml., 0·02 mole); the stirred liquid was then treated dropwise during 1—1½ hr. at 0—8° with *o*-nitrobenzenesulphenyl chloride [3] (6·65 g., 0·035 mole) in acetone (50 ml.) and simultaneously with 3N-sodium hydroxide (13·3 ml., 0·04 mole), at a rate to keep the mixture just alkaline (no alkali was needed during the first 10—15 min.; traces of methanethiol were liberated). The resulting suspension was made just acid with 1—2 drops of dilute hydrochloric acid and set aside at room temperature for 1 hr., and the solid filtered off and rinsed with a few drops of acetone (solid R). Spontaneous evaporation of the filtrate at room temperature gave a deep scarlet residue, which was rinsed with a little water, and allowed to drain and dry. It was dissolved in successive portions of cold acetone (2 × 15; 2 × 10 ml.), the solution decanted from a little undissolved solid S, and the solvent allowed to evaporate. A solution of the residue in warm benzene (6 × 5 ml.) slowly deposited deep-scarlet crystals (2·95—3·8 g.; 35—45%); a further crystallisation from benzene–light petroleum gave S-*methyl*-N-o-*nitrobenzenesulphenyl*isothiourea, scarlet prisms, m. p. 108—110° [Found: C, 39·7; H, 4·2; N, 17·0; S, 25·8%; *M* (cryoscopically, in thymol), 225. $C_8H_9O_2N_3S_2$ requires C, 39·5; H, 3·7; N, 17·3; S, 26·3%; *M*, 243].

Residue R (3—4 g.) was mainly inorganic; it was suspended in water (100 ml.), and the undissolved orange solid (0·2—0·5 g.) collected and crystallised from acetone or benzene, giving di-*o*-nitrophenyl disulphide, m. p. and mixed m. p. 196—197°. In some experiments the residue R consisted of the disulphenyl*iso*thiourea, m. p. and mixed m. p. 153—155° (see below). Solid S was impure di-*o*-nitrophenyl disulphide.

In experiments employing quicker addition (20—30 min.), mono- and di-sulphenylated (see below) *iso*thiourea were produced together (in approx. 20 and 15% yield, respectively) and were separated by fractional crystallisation from benzene, the monosubstituted product separating first. In one experiment, the *NN'*-disubstituted *iso*thiourea was formed almost exclusively.

S-*Methyl*-NN'-*di*-o-*nitrobenzenesulphenyl*isothiourea.—(*a*) A stirred solution of *S*-methyl*iso*thiourea (0·04 mole; prepared as above) was treated during 1½—2 hr. at 0—8° with the acid chloride (17 g., 0·09 mole) and 3N-sodium hydroxide (23·3 ml., 0·07 mole). The precipitate (T) was removed and the filtrate allowed to evaporate at room temperature. The separate aqueous layer was decanted from the red residue, which was rinsed with water, drained, and dried. Crystallisation from hot benzene (12 ml. per g.) gave prisms (m. p. 150—152°; 6·35 g., 40%); further crystallisation from benzene and from acetone gave S-*methyl*-NN'-*di*-o-*nitrobenzenesulphenyl*isothiourea, m. p. 153—155° (Found: C, 42·6, 42·7; H, 3·1, 3·0; N, 13·8; S, 23·8%; *M* (cryoscopically in naphthalene), 375. $C_{14}H_{12}O_4N_4S_3$ requires C, 42·4; H, 3·0; N, 14·1; S, 24·2%; *M*, 396). When crystallised from benzene only, the product had the same m. p., but gave high analyses for carbon. The final mother-liquors (acetone) contained small quantities of monosulphenylated *iso*thiourea. Solid T consisted of much inorganic material mixed mainly with di-*o*-nitrophenyl disulphide (up to 4·15 g., 30%).

In experiments in which the 3N-alkali was added at a rate which kept the mixture alkaline,

[1] Fairfull, Low, and Peak, *J.*, 1952, 742.
[2] Bogert and Stull, *Org. Synth.*, Coll. Vol. I, 1941, p. 220; Hubacher, *ibid.*, Coll. Vol. II, 1943, p. 455.

the granular precipitate afforded up to 10% of (III; R = Me; R′ = *o*-NO_2·C_6H_4). The added sulphenyl chloride reappeared mostly as *o*-nitrophenyl *o*-nitrobenzenethiolsulphonate (50%), yellow platelets, m. p. and mixed m. p. 139—141° (from benzene). (Found: C, 42·2; H, 2·6; N, 8·0; S, 18·3. Calc. for $C_{12}H_8O_6N_2S_2$: C, 42·35; H, 2·35; N, 8·2; S, 18·8%).

(*b*) *S*-Methyl-*N*-*o*-nitrobenzenesulphenyl*iso*thiourea (1·22 g., 0·005 mole) in acetone (10 ml.) was treated with sulphenyl chloride (0·006 mole)–N-sodium hydroxide (0·006 mole) during 90 min. The product, isolated and fractionated as before, gave up to 66% yields of the disulphenyl derivative, m. p. and mixed m. p. 153—154°.

Attempted demethylation of *S*-methyl-*N*-*o*-nitrobenzenesulphenyl- or *S*-methyl-*NN*′-di-*o*-nitrobenzenesulphenyl-*iso*thiourea by Fairfull, Low, and Peak's method [2] gave dark liquids (within 5—8 min.), from which only di-*o*-nitrophenyl disulphide, m. p. and mixed m. p. 197—198°, could be isolated (in 60 and 50% yield, respectively).

S-*Benzyl*-N-*o*-*nitrobenzenesulphenyl*iso*thiourea*.—A solution of *S*-benzyl*iso*thiuronium chloride (4·05 g., 0·02 mole) in warm water (15 ml.) was diluted with acetone (60 ml.) and cooled, and 3N-sodium hydroxide (3·3 ml., 0·01 mole) added. The stirred clear liquid was treated during 1 hr. with *o*-nitrobenzenesulphenyl chloride (0·015 mole) and 3N-sodium hydroxide (0·015 mole) in the usual way, the mixture being kept just alkaline. The deep-red solution was set aside to evaporate at room temperature, the resulting aqueous layer decanted, and the solid crystallised twice from benzene, and once from 1 : 1 acetone–benzene giving dark scarlet scales of S-*benzyl*-N-*o*-*nitrobenzenesulphenyl*iso*thiourea* (25 g.; 52%), m. p. 111—113° (Found: C, 52·7; H, 4·2; N, 13·1; S, 19·8. $C_{14}H_{13}O_2N_3S_2$ requires C, 52·7; H, 4·1; N, 13·2; S, 20·1%).

S-*Benzyl*-NN′-*di*-o-*nitrobenzenesulphenyl*iso*thiourea*.—Interaction of *S*-benzyl*iso*thiourea (0·02 mole.; water–acetone–alkali), *o*-nitrobenzenesulphenyl chloride (0·06 mole), and 3N-alkali (0·06 mole) during 2 hr. (as described immediately above) gave two phases containing much suspended solid, which was collected after storage overnight (Filtrate, F). After being washed with cold water and dried, the solid was crystallised from boiling benzene (25 ml.) (yield, 5·30 g., 56%) and then from acetone (10 ml.) giving orange-red prisms of S-*benzyl*-NN′-*di*-o-*nitrobenzenesulphenyl*iso*thiourea*, m. p. 146—148° (Found: C, 50·9; H, 3·4; N, 11·8; S, 20·7; $C_{20}H_{16}O_4N_4S_3$ requires C, 50·8; H, 3·4; N, 11·9; S, 20·3%). Evaporation of the deep-red layer of filtrate F gave small quantities of the disulphide (R′S·SR′) and more disulphenylated thiourea (6—12%).

The following experiments gave di-*o*-nitrophenyl disulphide as main product (% recovery in parentheses): (i—iv) Interaction of *o*-nitrobenzenesulphenamide [4] and phenyl *iso*thiocyanate (1·5 mole or large excess) in triethylamine (used as solvent or in catalytic quantities) at 95° during 1·5 hr. (60—75%); interaction of *o*-nitrobenzenesulphenyl chloride and (v) phenylthiourea (1 mole) in boiling benzene (80%), or (vi) thiourea (1·5 mole) in pyridine at 75° (during 30 min.) (90%); *o*-nitrobenzenesulphenamide was recovered (88%) after treatment with phenyl *iso*thiocyanate in the presence of sodium (1 equiv.) previously dissolved in acetone (15 min. at b. p. of solvent).

We thank the Council of the Chemical Society for a grant from the Research Fund.

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[*Received, October 31st*, 1957.]

[4] Zincke and Farr, *Annalen*, 1912, **391**, 55, 75.

XUM

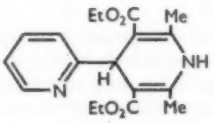
313. *The Synthesis of 2 : 4′-Dipyridyl and Some Derivatives.*

By R. F. Homer.

Several synthetic routes to 2 : 4′-dipyridyl derivatives have been examined. The parent base has been unambiguously synthesised by oxidation of 1 : 8-phenanthroline and decarboxylation of the resulting 2 : 4′-dipyridyl-3 : 3′-dicarboxylic acid. The Hantzsch reaction proceeds well with pyridine-2- and -4-aldehydes and acetoacetic ester, and provides a route to 2 : 6-dimethyl-2′ : 4- and -4 : 4′-dipyridyl. 1-4′-Pyridyl*iso*quinoline has also been prepared.

A DIPYRIDYL, m. p. 61°, was isolated by Smith [1] from among the products of the treatment of pyridine with sodium. Smith assigned the 3 : 4′-structure to this base because on oxidation it was alleged to give a mixture of *iso*nicotinic and nicotinic acid. Morgan and Burstall [2] isolated the same dipyridyl from the treatment of pyridine with ferric chloride and also described it as the 3 : 4′-isomer. More recently Krumholtz [3] has shown that it is found among the products of pyrolysis of pyridine, and oxidised it to a mixture of *iso*nicotinic and picolinic acid. On these grounds, and with supporting evidence from ultraviolet absorption data, Krumholtz concluded that the dipyridyl, m. p. 61·5° (picrate, m. p. 215°), is the 2 : 4′-isomer. In order conveniently to obtain a quantity of authentic 2 : 4′-dipyridyl a number of synthetic routes have been examined, and the base and a number of its derivatives have now been unambiguously synthesised. The properties of the synthetic material confirm Krumholtz's conclusions.

The Hantzsch reaction with pyridine aldehydes does not appear to have been reported. However, pyridine-2-aldehyde readily condensed with ethyl acetoacetate and ammonia to give 3 : 5-diethoxycarbonyl-1 : 4-dihydro-2 : 6-dimethyl-2′ : 4-dipyridyl (I) which on



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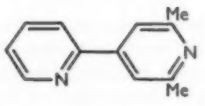
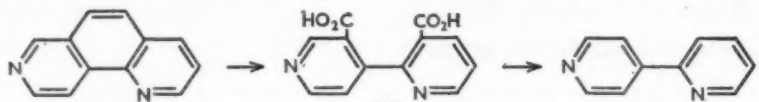


(II)

oxidation with nitric acid, followed by hydrolysis and decarboxylation, gave 2 : 6-dimethyl-2′ : 4-dipyridyl (II). Incidentally it was found that an analogous series of reactions carried out with pyridine-4-aldehyde gave 2 : 6-dimethyl-4 : 4′-dipyridyl.

Attempts to convert the base (II) into 2 : 4′-dipyridyl by oxidation to the acid followed by decarboxylation were not encouraging and this route was not further pursued when it became clear that a synthesis by way of 1 : 8-phenanthroline (III) was more profitable.



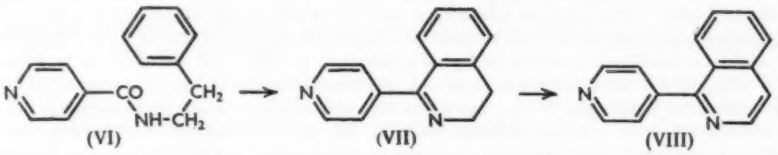
(III) (IV) (V)

Although the synthesis of this phenanthroline by a Skraup reaction with 5-amino*iso*quinoline has been reported by Misani and Bogert,[4] their yield was only 5%; but modifications in the method have now improved it to 35%, making this route a feasible preparative one. 1 : 8-Phenanthroline with permanganate gave 2 : 4′-dipyridyl-3 : 3′-dicarboxylic acid (IV) which could not be decarboxylated satisfactorily by distillation with lime but on

[1] Smith, *J. Amer. Chem. Soc.*, 1924, **46**, 419.
[2] Morgan and Burstall, *J.*, 1932, 20.
[3] Krumholtz, *J. Amer. Chem. Soc.*, 1951, **73**, 3487, 4449.
[4] Misani and Bogert, *J. Org. Chem.*, 1945, **10**, 358.

treatment with copper bronze in nitrobenzene was smoothly converted into 2 : 4′-dipyridyl (V).

1-2′-Pyridyl*iso*quinoline has recently been reported by Irving and Hampton,[5] who cyclised *N*-phenethylpicolinamide. By a similar cyclisation of *N*-phenethyl*iso*nicotinamide (VI) there is obtained 1-4′-pyridyl*iso*quinoline (VIII) by way of the dihydro-



compound (VII). Oxidation of the base (VIII) with permanganate gave a mixture of acidic products which on distillation with lime gave a mixture of volatile products among which only pyridine could be identified.

The bases described have been quaternised with methyl iodide.

Experimental

3 : 5-*Diethoxycarbonyl*-1 : 4-*dihydro*-2 : 6-*dimethyl*-2′ : 4-*dipyridyl*.—Pyridine-2-aldehyde (43 g.), ethyl acetoacetate (104 g.), ethanol (50 c.c.), and ammonia (20·5 c.c.; *d* 0·880) were mixed and heated slowly to 80° for 4 hr.; more ammonia (5 c.c.) was then added, and heating was continued for a further 4 hr. The pale fawn prisms which separated were filtered off and washed with a little ethanol followed by ether. The *ester* (62·5 g.) had m. p. 196—198° unchanged on crystallisation from ethanol (Found: C, 65·9; H, 6·8; N, 8·7. $C_{18}H_{22}O_4N_2$ requires C, 65·4; H, 6·7; N, 8·5%).

3 : 5-*Diethoxycarbonyl*-2 : 6-*dimethyl*-2′ : 4-*dipyridyl*.—The above dihydro-compound (55 g.) was warmed in water (57 c.c.) and sulphuric acid (9 c.c.; *d* 1·84) to 40°, and nitric acid (11 c.c.; *d* 1·4) added all at once. When the vigorous reaction had subsided the mixture was cooled with added ice and basified with ammonia solution. The solid was filtered off, washed with water, and crystallised from aqueous ethanol to yield the *ester* (22 g.), m. p. 99—100° (Found: C, 65·9; H, 6·4. $C_{18}H_{20}O_4N_2$ requires C, 65·8; H, 6·1%).

2 : 6-*Dimethyl*-2′ : 4-*dipyridyl*.—3 : 5-Diethoxycarbonyl-2 : 6-dimethyl-2′ : 4-dipyridyl (20 g.) was heated to the b. p. with ethanol (45 c.c.). Potassium hydroxide (10 g.) in ethanol (45 c.c.) was added in three portions during ½ hr. The mixture was heated under reflux for ½ hr. more and evaporated to dryness in an evaporating dish. The residue was ground with calcium oxide (40 g.) and distilled at 400—500°. The crude distillate (10 g.) gave on redistillation 2 : 6-*dimethyl*-2′ : 4-*dipyridyl* (6·0 g.), b. p. 180—183°/27 mm. (Found: C, 78·3; H, 6·9; N, 15·2. $C_{12}H_{12}N_2$ requires C, 78·3; H, 6·5; N, 15·2%). The *picrate* melted at 202° (Found: N, 17·2. $C_{18}H_{15}O_7N_5$ requires N, 17·0%).

2 : 6-*Dimethyl*-4 : 4′-*dipyridyl*.—This was prepared by a similar reaction sequence from pyridine-4-aldehyde. The *base* had b. p. 178°/17 mm. and solidified (Found: N, 15·2%). The intermediate 3 : 5-*diethoxycarbonyl*-1 : 4-*dihydro*-2 : 6-*dimethyl*-4 : 4′-*dipyridyl*, crystallised from aqueous ethanol, had m. p. 195° (Found: C, 65·1; H, 6·7; N, 7·9%). 3 : 5-*Diethoxycarbonyl*-2 : 6-*dimethyl*-4 : 4′-*dipyridyl* had m. p. 112° (from aqueous ethanol) (Found: C, 66·1; H, 6·5; N, 8·8%).

2 : 6-*Dimethyl*-2′ : 4-*dipyridyl Monomethiodide*.—2 : 6-Dimethyl-2′ : 4-dipyridyl (1·4 g.), ethanol (15 c.c.), water (2 c.c.), and methyl iodide (3 c.c.) were stirred under reflux for 16 hr. When the cooled mixture was poured into dry ether (50 c.c.) the *monomethiodide* separated; it had m. p. 232—234° after crystallisation from ethanol (Found: N, 8·5; I, 38·9. $C_{13}H_{15}N_2I$ requires N, 8·4; I, 38·0%).

2 : 6-*Dimethyl*-2′ : 4-*dipyridyl Dimethiodide*.—The above monomethiodide (0·7 g.) was heated with 95% ethanol (20 c.c.) and methyl iodide (5 c.c.) in a sealed tube at 100—110° for 6 hr. The mixture was evaporated to dryness and the residue triturated with acetone to give the *dimethiodide* (0·65 g.), m. p. 222° (Found: N, 5·9; I, 55·0. $C_{14}H_{18}N_2I_2$ requires N, 6·0; I, 54·3%).

[5] Irving and Hampton, *J.*, 1955, 430.

2 : 6-*Dimethyl*-4 : 4′-*dipyridyl Dimethiodide*.—The base (2·5 g.), 95% ethanol (75 c.c.), and methyl iodide (10 c.c.) were stirred under reflux for 8 hr. The solid was filtered off and washed with acetone, giving the *dimethiodide*, m. p. 310° (decomp.) (Found: N, 6·0%).

1 : 8-*Phenanthroline*.—5-Amino*iso*quinoline (54 g.) was added to a mixture of sulphuric acid (720 c.c.; *d* 1·84), water (230 c.c.), glycerol (171 c.c.), and arsenic acid solution (150 c.c.; *d* 1·95). The mixture was stirred at 140° for 2½ hr., cooled, poured on ice, and made alkaline with aqueous ammonia (*d* 0·880). The mixture was stirred with chloroform (500 c.c.) for 1 hr., then filtered, and the lower layer separated and evaporated to give a residue of crude 1 : 8-phenanthroline (29 g.) which on distillation yielded 24·5 g. of product, b. p. 138—140°/0·3 mm., m. p. 105—108°.

2 : 4′-*Dipyridyl*-3 : 3′-*dicarboxylic Acid*.—1 : 8-Phenanthroline (20 g.) was suspended in water containing sodium hydroxide (8·5 g., 2 mol.) at 80—85°, and potassium permanganate (*ca.* 70 g.) added at such a rate as to keep the temperature at 80—95°, the end-point of the reaction being marked by a persistent pink colour on spotting on filter-paper. The mixture was filtered, and the filtrate evaporated to 100 c.c. and adjusted to pH 3·2 with hydrochloric acid. The *acid* (16·5 g.) separated. Crystallisation from water gave material of m. p. 275° (rapid heating) (Found: C, 59·5; H, 3·5; N, 11·4. $C_{12}H_8O_4N_2$ requires C, 59·0; H, 3·3; N, 11·4%).

2 : 4′-*Dipyridyl*.—2 : 4′-Dipyridyl-3 : 3′-dicarboxylic acid (16·5 g.) was added during 1 hr. to a stirred mixture of nitrobenzene (100 c.c.) and copper bronze (0·5 g.) at 205—210°. Carbon dioxide was evolved. The mixture was heated at 205—210° for 1 hr. after the end of the addition, cooled to 100°, treated with carbon, and filtered. The filtrate was extracted with 2N-hydrochloric acid (3 × 50 c.c.), and the combined acid extracts were washed with ether and basified with sodium hydroxide solution. The base was extracted with chloroform and distilled, to give 2 : 4′-dipyridyl, b. p. 148—150°/11 mm., m. p. 59—60°, raised by crystallisation from light petroleum (b. p. 60—80°) to 61·5°. The picrate had m. p. 214°.

2 : 4′-*Dipyridyl Mono- and Di-methiodide*.—2 : 4′-Dipyridyl (2 g.), 95% ethanol (20 c.c.), and methyl iodide (4 c.c.) were heated at 100—110° for 7½ hr. The solid was filtered off and fractionally crystallised from 95% ethanol, to give the *monomethiodide*, m. p. 188—190° (1·0 g.) (Found: N, 8·7. $C_{11}H_{11}N_2I,H_2O$ requires N, 8·8%), and, as the less soluble fraction, the dimethiodide, m. p. 225° (0·8 g.) (Found: N, 6·5. Calc. for $C_{12}H_{14}N_2I_2$: N, 6·4%).

N-*Phenethyliso*nicotinamide.—Ethyl *iso*nicotinate (75 g.) and phenethylamine (90 g.; 1·5 mol.) were heated at 170—180°, and the ethanol (22 c.c.) distilled off. Heating was continued for 6 hr. After cooling, the residue crystallised from benzene to give the *compound* (117 g.), m. p. 120° (Found: C, 73·7; H, 6·3; N, 12·6. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%).

3 : 4-*Dihydro*-1-4′-*pyridyliso*quinoline.—*N*-Phenethyl*iso*nicotinamide (39 g.) was dissolved in benzene (400 c.c.). Phosphorus pentachloride (45 g.) was added, and the mixture stirred under reflux for 1 hr. The mixture was cooled, and powdered aluminium chloride (45 g.) added, a vigorous reaction ensuing. The mixture was stirred under reflux for 3 hr. more, the benzene distilled off, and the residue decomposed by adding water (200 c.c.). The aqueous solution was strongly basified with sodium hydroxide solution and extracted with chloroform. This extract was extracted with 2N-hydrochloric acid (3 × 100 c.c.), and the combined acid extracts were heated under reflux for 7 hr. to hydrolyse an unreacted amide. On basification with sodium hydroxide solution an oil separated which was extracted with chloroform and distilled. The *base* (13 g.) distilled at 145—148°/0·3 mm. and solidified. Crystallisation from light petroleum (b. p. 60—80°) gave material of m. p. 56° (Found: C, 81·3; H, 6·0; N, 12·8. $C_{14}H_{12}N_2$ requires C, 80·8; H, 5·8; N, 13·4%).

1-4′-*Pyridyliso*quinoline.—The dihydro-base (4 g.) was heated at 260—280° for 7 hr. with 5% palladium–carbon (4·5 g.). Extraction of the mixture with ethanol gave a solid *base* which, recrystallised from light petroleum (b. p. 60—80°), had m. p. 91° (2·5 g.) (Found: C, 82·1; H, 5·3. $C_{14}H_{10}N_2$ requires C, 81·6; H, 4·9%).

3 : 4-*Dihydro*-1-4′-*pyridyliso*quinoline *Dimethiodide*.—The base (3·5 g.) was heated in a sealed tube at 100—110° for 7 hr. with 95% ethanol (50 c.c.) and methyl iodide (10 g.). The solid which separated was filtered off and crystallised from aqueous ethanol to give the *dimethiodide* (8·0 g.), m. p. 245° (Found: C, 37·6; H, 4·1; N, 5·7; I, 51·7. $C_{16}H_{18}N_2I_2,H_2O$ requires C, 37·6; H, 3·9; N, 5·5; I, 49·8%). In a similar manner was obtained 1-4′-*pyridyliso*quinoline *dimethiodide*, m. p. 248° from aqueous ethanol (Found: C, 37·7; H, 3·5; N, 5·6; I, 50·9. $C_{16}H_{16}N_2I_2,H_2O$ requires C, 37·8; H, 3·5; N, 5·5; I, 50·0%).

Oxidation of 1-4′-*Pyridyliso*quinoline *by Permanganate*.—The base (1·0 g.), potassium permanganate (2·2 g., 3 mol.), potassium hydroxide (0·5 g.), and water (100 c.c.) were heated at

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80—90° until the permanganate colour was discharged (10 min.). The mixture was filtered and evaporated to 15 c.c., and the pH adjusted to 3·2 with hydrochloric acid. The solid acidic product (0·52 g.) was filtered off, dried, mixed with calcium oxide (2 g.), and distilled at dull red heat. The distillate was dissolved in ethanol and treated with picric acid. Repeated recrystallisation of the crude picrate gave a small yield of pyridine picrate, m. p. 163—166° undepressed on admixture with an authentic sample of m. p. 167°.

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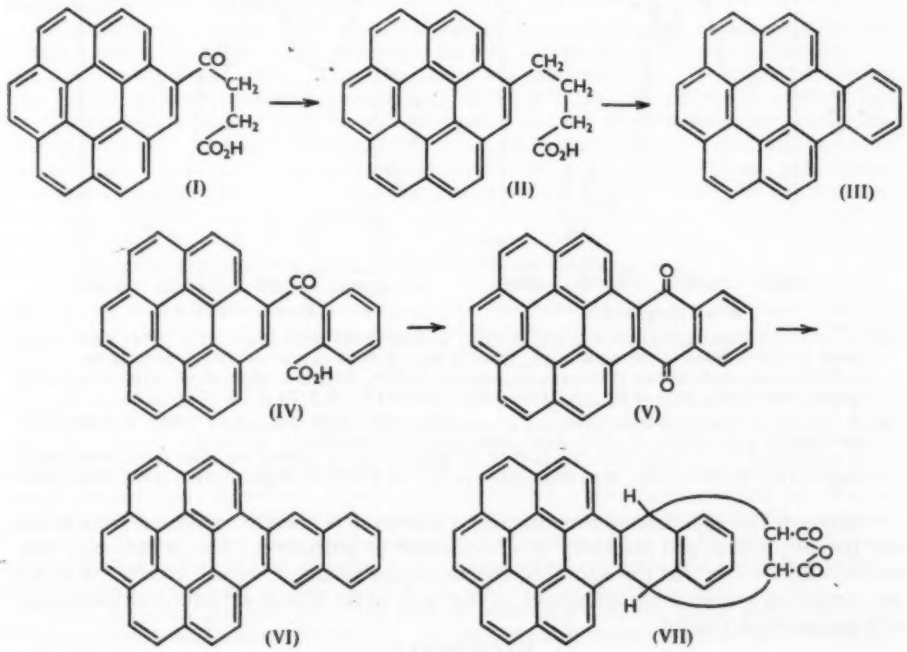
314. 1 : 2-*Benzocoronene and Naphtho*(2′ : 3′-1 : 2)*coronene.*

By E. CLAR and M. ZANDER.

Coronene, condensed with succinic anhydride, gives the keto-acid (I) which on reduction and cyclisation in sodium chloride–zinc chloride affords 1 : 2-benzocoronene (III). Coronene was also condensed with phthalic anhydride to the keto-acid (IV); cyclisation then afforded the quinone (V) which was reduced to the naphthocoronene (VI); this adds maleic anhydride to give compound (VII).

CORONENE is now easily accessible from commercial perylene.[1] We have therefore started to synthesise systematically the benzologues of coronene. Coronene with succinic anhydride and aluminium chloride gives the keto-acid (I), reduced by the Huang-Minlon



method to the butyric acid (II), which cyclised in a melt of sodium chloride and zinc chloride, with simultaneous aromatisation of the newly formed ring, to 1 : 2-benzocoronene (III). This is pale yellow, as is coronene.

In attempts to condense coronene with phthalic anhydride and aluminium chloride,

[1] Clar and Zander, *J.*, 1957, 4616.

benzene and nitrobenzene proved unsuitable solvents. We therefore used *o*-dichlorobenzene which is described in patents [2] as a solvent for three-fold condensation of phthalic anhydride with coronene. A monocarboxylic acid (IV) was obtained which was easily cyclised to the monoquinone (V) by boiling benzoyl chloride. Its melting point and its vat are the same as those reported for the alleged triquinone.[2] Naphthocoronene (VI) was obtained by reduction of the quinone (V) with pyridine, zinc dust, and acetic acid. The yellow naphthocoronene showed acene character and added maleic anhydride, giving the adduct (VII).

The ultraviolet absorption spectra of the butyric acid (II) and of the adduct (VII) (Fig. 1) are of typical coronene form, the α-bands of the adduct being more intense, as is characteristic for cyclic alkyl derivatives. In passing from benzocoronene (III) to naphthocoronene (VI) (Fig. 2), the red shift of the *p*-bands (470 Å) is considerably greater than in passing from coronene to benzocoronene (345 Å). This accords with the asymmetric annellation effect in the pyrene and perylene series; [3] it shows that the spectral properties of condensed systems become increasingly acene-like when benzene rings are annellated linearly and asymmetrically.

Absorption max. (Å) *and* log ε (*in parentheses*).

FIG. 1.

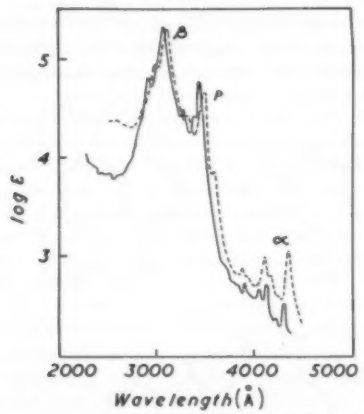


FIG. 2.

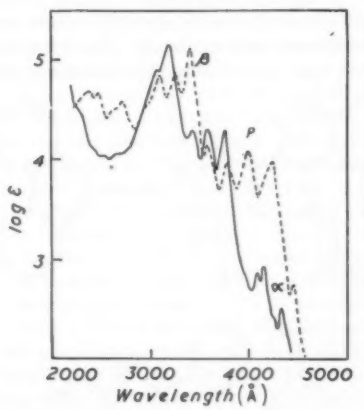


FIG. 1. (——) *γ-Coronenylbutyric acid* (II) *in* C_6H_6, α, 4300 (2·53), 4225 (2·40), 4120 (2·74), 4060 (2·69), 3900 (2·73); *p*, 3440 (4·78), 3390 (4·42), 3280 (4·48); β, 3080 (5·33); *in* EtOH, 2930 (4·80).
(– – –) *Maleic anhydride adduct* (VII), *dipotassium salt in* 50% EtOH, α, 4350 (3·06), 4160 (2·82), 4100 (2·99), 3880 (2·89), 3600 (3·86); *p*, 3480 (4·65), 3320 (4·41); β, 3100 (5·28), 2980 (4·92).

FIG. 2. (——) 1 : 2-*Benzocoronene* (III) *in* C_6H_6, α, 4320 (2·50), 4140 (2·91), 4080 (2·85); *p*, 3760 (4·30), 3580 (4·30), 3430 (4·29); β, 3200 (5·15), 3080 (4·90). (*From* 3000 Å *in* EtOH.)
(– – –) *Naphtho*(2′ : 3′-1 : 2)*coronene* (VI) *in* C_6H_6, α, 4440 (2·74); *p*, 4230 (3·99), 4000 (4·09), 3790 (3·98), 3580 (4·16); β, 3410 (5·12); 3260 (4·88), 3100 (4·86); *in* EtOH, 2720 (4·60), 2480 (4·68), 2390 (4·70).

Although the naphthocoronene contains a system of 5 linearly condensed rings it has not the deep colour and reactivity of a benzologue of pentacene. This is obviously connected with the fact that this naphthocoronene cannot assume a Kekulé structure in which the pentacene system is not quinonoid, so that none of the Kekulé structures characteristic of a pentacene is possible.

EXPERIMENTAL

M. p.s were taken in evacuated capillaries. Microanalyses are by Mr. J. M. L. Cameron and Miss M. W. Christie.

γ-Coronenyl-γ-oxobutyric Acid (I).—Coronene (3 g.) was ground with succinic anhydride

[2] I.G. Farbenind. A.-G., F.P. 857,395/1939; General Aniline and Film Corp., U.S.P. 2,210,041/1939; *Chem. Zentr.*, 1941, I, 1096.
[3] Boggiano and Clar, *J.*, 1957, 2681; Clar and Willicks, *Annalen*, 1956, **601**, 193.

(1·1 g.) and suspended in a solution of aluminium chloride (6 g.) in nitrobenzene (30 ml.). After 4 hours' stirring the mixture was decomposed with ice and dilute hydrochloric acid and then boiled. The greenish-yellow precipitate (3·25 g.) was filtered off and washed with benzene, methanol, and dilute hydrochloric acid. The *keto-acid* formed flat yellow needles, m. p. 244—252° (decomp.), from chlorobenzene or xylene, gave a blue solution with sulphuric acid which soon changed to violet, and in xylene had an absorption band at 4440 Å (Found: C, 83·3; H, 4·2. $C_{28}H_{16}O_3$ requires C, 84·0; H, 4·0%).

γ-Coronenylbutyric Acid (II).—The acid (I) (2·4 g.), sodium hydroxide (0·72 g.), 90% hydrazine hydrate (0·9 ml.), and diethylene glycol (30 ml.) were refluxed for 1 hr., then water and excess of hydrazine hydrate were distilled off until the temperature rose to 200°. The mixture was then refluxed again for 3 hr. After cooling and dilution with water and hydrochloric acid, the solid was filtered off and washed with dilute hydrochloric acid and water. *γ-Coronenylbutyric acid* formed flat pale yellow needles (1·35 g.), m. p. 277—287° (decomp.) (from xylene), which dissolved in concentrated sulphuric acid to give a yellow-brown solution (Found: C, 87·1; H, 4·9. $C_{28}H_{18}O_2$ requires C, 87·0; H, 4·7%).

1 : 2-*Benzocoronene* (III).—A mixture of the acid (II) (0·8 g.), sodium chloride (6 g.), and zinc chloride (30 g.) was ground and heated at 300° for 45 min. The melt was dissolved in dilute acetic acid, and the residue filtered off and washed with water and aqueous ammonia (yield 0·65 g.). Sublimation below 300°/0·1 mm. yielded a yellow fraction which was discarded and then at 300—320°/0·1 mm. a material which after repeated recrystallisation from xylene gave yellow needles of 1 : 2-*benzocoronene*, m. p. 292—294°, which dissolved in hot concentrated sulphuric acid with a greenish-yellow colour (Found: C, 95·8; H, 4·3. $C_{28}H_{14}$ requires C, 96·0; H, 4·0%). When the melt was held at 270° for 15 min. a different product was obtained which showed absorption bands in xylene at 4420 and 4160 Å and dissolved in cold concentrated sulphuric acid with a red colour.

o-*Carboxybenzoylcoronene* (IV).—Finely powdered coronene (3 g.) and phthalic anhydride (1·65 g.) were suspended in *o*-dichlorobenzene (50 ml.), and powdered aluminium chloride (6 g.) was added at 50° with stirring. The temperature was increased to 65—70° and kept there for 3 hr. After decomposition with ice and hydrochloric acid the yellowish-green solid product was filtered off and washed with benzene, methanol, and hot dilute hydrochloric acid. The crude *acid* (3·4 g.) was dissolved in hot 0·5% potassium hydroxide solution (600 ml.) and after filtration precipitated with dilute hydrochloric acid (yield, 3 g.). Crystallisation from xylene gave yellow needles (2·48 g.), m. p. 297—299° (decomp.), which gave a violet solution with concentrated sulphuric acid soon changing to green and in xylene had an absorption band at 4400 Å (Found: C, 85·6; H, 3·8. $C_{33}H_{16}O_3$ requires C, 85·7; H, 3·6%). Concentration of the *o*-dichlorobenzene mother-liquor yielded less pure acid (0·85 g.).

Naphtho(2′ : 3′-1 : 2)*coronene*-1′ : 4′-*quinone* (V).—The keto-acid (IV) (0·5 g.), benzoyl chloride (0·5 ml.), and 1-chloronaphthalene (2 ml.) were refluxed for 1 hr., the colour changing from green to dark red. The *quinone* (0·44 g.) which crystallised on cooling was filtered off and washed with benzene and ether. It sublimed at 380°/0·3 mm. in dark red needles and, recrystallised from nitrobenzene, had m. p. 347—349° and gave a green solution in concentrated sulphuric acid and a violet vat (Found: C, 89·4; H, 3·4. $C_{33}H_{14}O_3$ requires C, 89·3; H, 3·3%).

Naphtho(2′ : 3′-1 : 2)*coronene* (VI).—The quinone (1 g.) was boiled in pyridine (50 ml.) with zinc dust (10 g.), under an air-trap, and concentrated acetic acid (2 ml.) was added. 80% Acetic acid (8 ml.) was dropped into the mixture during 3 hr. The solution became first deep orange-red and then pale yellow. It was poured into dilute hydrochloric acid and heated until the zinc dissolved. The residue (0·91 g.) was filtered off and washed with water and dilute aqueous ammonia. Crystallisation from xylene yielded yellow needles of the *naphthocoronene* (0·7 g.), m. p. 352—354°, which did not dissolve in cold concentrated sulphuric acid but gave a yellow-green solution on warming (Found: C, 95·9; H, 4·0. $C_{33}H_{16}$ requires C, 96·0; H, 4·0%).

Maleic Anhydride Adduct (VII).—The naphthocoronene (0·1 g.) and maleic anhydride (2 g.) in xylene (20 ml.) were refluxed for 45 min. The *adduct* which crystallised from the hot solution was decanted and washed with hot xylene and then with benzene. The yellow prisms, m. p. 358—360° (decomp.), did not dissolve in cold concentrated sulphuric acid (Found: C, 86·3; H, 3·9. $C_{36}H_{18}O_3$ requires C, 86·7; H, 3·6%).

One of us (M. Z.) is indebted to Rütgerswerke A.-G., Frankfurt/Main, for a scholarship.

UNIVERSITY OF GLASGOW. [*Received, November 25th,* 1957.]

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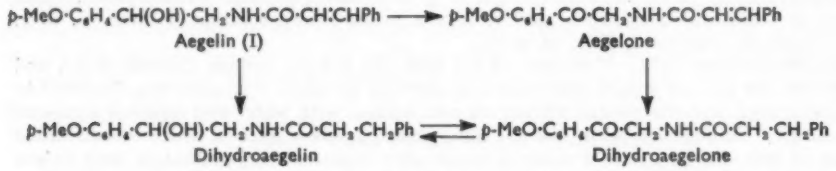
315. *The Structure of Aegelin.*

By R. N. Chakravarti and B. Dasgupta.

Details are provided for the proof of structure and synthesis of aegelin reported earlier.

Aegelin, isolated by Chatterjee and Bose [1] from the leaves of *Aegle marmelos* Correa, was believed by them to be a steroid, $C_{18}H_{18}O_4$. In preliminary communications,[2] however, we showed that it was nitrogenous ($C_{18}H_{19}O_3N$) and proved its structure as the (±)-*trans*-form of compound (I) by carrying out the reactions shown in the scheme and by synthesis of the four compounds shown there.



Chatterjee and Chaudhuri [3] recently adopted our formula and structure and reported alternative syntheses, but all without reference to our prior publications. We therefore record here details of our work.

Experimental

Modified Method for Isolation of Aegelin.—Air-dried powdered leaves (14 kg.) of *Aegle marmelos* were extracted repeatedly with cold 90% ethanol. The extract was mixed with filter-paper pulp, dried at 80°, and extracted with ether (Soxhlet) for about 80 hr. The extract was concentrated to *ca.* 1·5 l. and kept at 0° for a week, and the separated product collected, washed with ether, crystallised from ethyl acetate and then from ethanol–acetone, passed in ethanol through aluminium oxide, and finally crystallised from ethanol, giving aegelin as plates, m. p. 178—179° [Found: C, 72·7; H, 6·3; N, 4·45; OMe, 9·6; active H, 0·75%; *M* (Rast), 291. Calc. for $C_{18}H_{19}O_3N$: C, 72·7; H, 6·4; N, 4·7; 1OMe, 10·4; 2 active H, 0·67%; *M*, 297·3].

From mature leaves (November to March) the yield of aegelin is very low, but from young leaves (May to August) the yield is 0·15—0·2%. It has an absorption maximum at 275 mμ (log ε 4·42), as reported by Chatterjee and Bose,[1] but also maxima at 212 and 219 mμ (log ε 4·36, 4·36). *trans-N*-Methylcinnamamide has similar maxima at 218 and 270 mμ (log ε 4·18, 4·39). Aegelin evolves little hydrogen selenide when heated with selenium according to Chatterjee and Bose's method.[1]

Aegelin Esters.—Aegelin (0·1 g.), acetic anhydride (2 c.c.), and pyridine (2 drops) were heated on a water-bath for 4 hr. Alternatively, aegelin (0·6 g.), acetic anhydride (2 c.c.), and sodium acetate (0·6 g.) were heated under reflux for 20 min. The *acetate*, crystallised from ethyl acetate and then aqueous methanol, had m. p. 123—125° (Found: C, 71·1; H, 6·5; Ac, 13·5. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·2; 1Ac, 12·7%). Chatterjee and Bose's product,[1] of m. p. 159—160°, appears to have been a mixture.

The *benzoate* was prepared from benzoyl chloride (1·5 c.c.) and aegelin (0·6 g.) in pyridine (12 c.c.) at room temperature overnight and crystallised from ethanol in needles, m. p. 147—148° [Found: C, 75·0; H, 5·4; N, 3·1; OMe, 5·2; Bz, 28·1%; *M* (Rast), 419. $C_{25}H_{23}O_4N$ requires C, 74·8; H, 5·8; N, 3·5; 1OMe, 7·7; 1Bz, 26·2%; *M*, 401·44].

Aegelone.—Chromic acid (0·2 g.) was added in small lots with shaking during 4 hr. to a solution of aegelin (0·5 g.) in glacial acetic acid (25 c.c.) at the room temperature. Acetic acid was distilled off under reduced pressure, and the residue diluted with water. The separated solid was filtered off and repeatedly crystallised from ethanol, giving *aegelone* as colourless

[1] Chatterjee and Bose, *J. Indian Chem. Soc.*, 1952, **29**, 425.
[2] Chakravarti and Dasgupta, *Chem. and Ind.*, 1955, 1632; *Bull. Calcutta School Trop. Med.*, 1956, **4**, 69, 123, 167; Chakravarti, Ann. Rept. Calcutta School Trop. Med., 1955—56, 70; Dasgupta, D.Phil. (Science) Thesis, Calcutta, 1956.
[3] Chatterjee and Chaudhuri, *Science and Culture*, 1957, **23**, 155.

needles, m. p. 159—160° (0·35 g.) (Found: C, 73·6; H, 5·8; N, 4·25. $C_{18}H_{17}O_3N$ requires C, 73·2; H, 5·8; N, 4·7%).

Aegelone does not colour Schiff's reagent nor does it respond to the Angeli–Rimini test for aldehydes. When heated on a water-bath it reduces ammoniacal silver nitrate solution within a minute. The *semicarbazone* is obtained in needles, m. p. 234—235° (decomp.) (Found: C, 64·3; H, 5·6; N, 15·2. $C_{19}H_{20}O_3N_4$ requires C, 64·8; H, 5·7; N, 15·9%). The ultraviolet absorption spectrum of aegelone (max. at 280 mμ; log ε 4·67) resembles that of ω-amino-*p*-methoxyacetophenone hydrogen sulphate (max. at 282 mμ; log ε 4·27).

Dihydroaegelin.—Aegelin (0·5 g.) was shaken in acetic acid (25 c.c.) solution with Adams catalyst (50 mg.) under hydrogen [absorption, complete in 15 min.: 42 c.c. (N.T.P.); 1 mol. = 37·7 c.c.]. After filtration acetic acid was distilled off under reduced pressure, and the residue diluted with water. The separated *dihydroaegelin* crystallised from ethanol in leaflets, m. p. 140—141° (0·33 g.) (Found: C, 72·4; H, 7·15; N, 4·4. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·1; N, 4·7%). Dihydroaegelin, like aegelin, does not reduce ammoniacal silver nitrate solution when heated on a water-bath for several minutes.

Dihydroaegelone.—This was prepared, in the same way as aegelone, by chromic acid oxidation of dihydroaegelin. *Dihydroaegelone* crystallised from ethanol in needles, m. p. 126—127° (Found: C, 72·9; H, 6·5; N, 4·5. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7%). It reduces ammoniacal silver nitrate solution on a water-bath in a few minutes, and gives a *semicarbazone* (needles), m. p. 138—140° (Found: C, 64·0; H, 6·4; N, 15·0. $C_{19}H_{22}O_3N_4$ requires C, 64·4; H, 6·3; N, 15·8%).

Dihydroaegelone was also prepared by partial hydrogenation of aegelone (0·5 g.) in acetic acid (20 c.c.) over Adams catalyst (50 mg.). Hydrogenation was stopped when the rate of absorption became slow [absorption, 45 c.c. (N.T.P.); 1 mol. = 37·9 c.c.]. The product had m. p. 126—127°.

Catalytic Hydrogenation of Dihydroaegelone.—A solution of dihydroaegelone (0·5 g.) in glacial acetic acid (25 c.c.) was shaken with Adams catalyst (50 mg.) under hydrogen [absorption, complete in 30 min.: 40 c.c. (N.T.P.); 1 mol. = 37·7 c.c.]. Dihydroaegelin obtained in this way and crystallised from ethanol had m. p. 140—141°.

Alkaline Permanganate Oxidation of Aegelin.—Potassium permanganate (4 g.) and potassium hydroxide (0·5 g.) in water (100 c.c.) were gradually added to a boiling aqueous suspension of aegelin (1 g.) in water (10 c.c.). The excess of permanganate was then decomposed with methanol, the whole filtered, and the filtrate concentrated to 20 c.c., cooled, and acidified with hydrochloric acid. A white precipitate (0·4 g.) was obtained. It was separated into two crops by repeated fractional crystallisations from hot water.

The less soluble crop yielded needles (from hot water), m. p. 183—184° [Found: C, 63·0; H, 5·4; OMe, 19·8%; *M* (Rast), 150. Calc. for $C_8H_8O_3$: C, 63·15; H, 5·3; OMe, 20·4%; *M*, 152·14]. It was identified as *p*-anisic acid (mixed m. p.).

The more soluble crop yielded glistening plates (from water), m. p. 120—121° [Found: C, 68·6; H, 5·1%; *M* (Rast), 125. Calc. for $C_7H_6O_2$: C, 68·8; H, 4·95%; *M*, 122]. It was identified as benzoic acid (mixed m. p.).

In a second experiment the oxidation was carried with distillation. The clear aqueous distillate yielded benzaldehyde 2 : 4-dinitrophenylhydrazone (60 mg.), m. p. and mixed m. p. 235°.

Hydrolysis of Aegelin with Hydrochloric acid.—Aegelin (2 g.) was refluxed for 8 hr. with 90% ethanol (72 c.c.) and concentrated hydrochloric acid (12 c.c.), and then distilled in steam. The oily globules from the second fraction of the distillate were taken up in ether, washed with sodium hydrogen carbonate solution, then water, and dried. The oil (0·427 g.) obtained on evaporation of the ether was warmed with aqueous semicarbazide hydrochloride and sodium acetate containing a little ethanol for 0·5 hr. Overnight oily globules with a few crystals separated. The aqueous solution was removed and the remaining product washed with water, drained, and treated with ether to dissolve the adhering oil. The crystalline product (45 mg.) obtained was purified by crystallisation from ethanol and identified as *p*-anisaldehyde semicarbazone (plates), m. p. and mixed m. p. 203—204° (Found: C, 56·2; H, 5·5; N, 20·9; OMe, 15·25. Calc. for $C_9H_{11}O_2N_3$: C, 55·95; H, 5·7; N, 21·75; OMe, 16·1%). The ether washings from the semicarbazone on evaporation gave an oil (smell of ester) which was hydrolysed with 10% ethanolic potassium hydroxide, freed from ethanol, and acidified with hydrochloric acid; *trans*-cinnamic acid (0·19 g.) separated and crystallised from hot water as plates, m. p. and mixed m. p. 133—134°.

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The residual liquid obtained after removal of volatile matter by steam was extracted with ether (extract A). The aqueous layer, on being made alkaline, became turbid, with evolution of ammonia. On extraction with ether and removal of the solvent a minute amount of basic crystals was obtained which in acid solution gave a creamy precipitate with Meyer's reagent.

In one experiment the acid solution after steam-distillation and extraction with ether was evaporated to dryness and the dry salt obtained was heated with alkali. The gases evolved were absorbed in ethanol and allowed to react with 1-chloro-2 : 4-dinitrobenzene: 2 : 4-dinitroaniline was obtained, and had m. p. and mixed m. p. 175—176°, confirming the presence of ammonia in the products of hydrolysis of aegelin.

The ethereal extract (A) was washed with sodium hydrogen carbonate solution. The alkaline extract on acidification with hydrochloric acid yielded *trans*-cinnamic acid (0·32 g.) which crystallised from hot water in plates, m. p. and mixed m. p. 133—134° [Found: C, 72·8; H, 5·25%; *M* (Rast), 147; equiv., 146·9. Calc. for $C_9H_8O_2$: C, 73·0; H, 5·4%; *M*, equiv., 148].

*ω-Amino-*p*-methoxyacetophenone Hydrogen Sulphate.*—This was prepared by a modification of Kindler and Peschke's method.[4] *p*-Methoxybenzoyl cyanide (1·3 g.) in acetic acid (15 c.c.) was hydrogenated over Adams catalyst (0·1 g.) at atmospheric pressure and room temperature. The hydrogenation was stopped after absorption of 2 mols. of hydrogen (20 min.). After filtration the dark brown acetic acid solution was treated with concentrated sulphuric acid (0·46 c.c.) and diluted with ether; ω-amino-*p*-methoxyacetophenone hydrogen sulphate (1·3 g.) separated. Crystallised from acetic acid, it had m. p. 167—168°.

*ω-Cinnamoylamino-*p*-methoxyacetophenone.*—An aqueous solution of the preceding sulphate (0·3 g.) was treated with *trans*-cinnamoyl chloride (0·3 c.c.) at room temperature. 10% Sodium hydroxide solution was added gradually with shaking till the mixture gave an ammoniacal smell and became pink. Then more cinnamoyl chloride (0·2 c.c.) was added and the whole shaken till the pink colour disappeared. The mixture was again made alkaline. The separated solid was collected and crystallised from ethanol, giving ω-cinnamoylamino-*p*-methoxyacetophenone as needles (0·2 g.), m. p. 159—160° (Lister and Robinson [5] give m. p. 153—154°) undepressed on admixture with aegelone (Found: C, 73·4; H, 5·9%). It gave a semicarbazone, m. p. and mixed m. p. 234—235° (decomp.).

As described by Lister and Robinson,[5] under the dehydrating action of concentrated sulphuric acid, aegelone also gives 5-*p*-methoxyphenyl-2-styryloxazole which in solution exhibits intense blue fluorescence.

p-*Methoxy-ω-β-phenylpropionamidoacetophenone.*—β-Phenylpropionyl chloride (0·3 c.c.) was added to an aqueous solution of the sulphate (0·3 g.), followed by 10% sodium hydroxide solution with shaking and cooling. The initial red colour disappeared on shaking and a pasty mass separated which gradually disintegrated into small lumps. When distinctly alkaline, the separated brick-red solid crystallised from ethanol, giving p-*methoxy-ω-β-phenylpropionamidoacetophenone* as needles (0·2 g.), m. p. and mixed m. p. with dihydroaegelone, 126—127° (Found: C, 72·7; H, 6·5; N, 4·5%). The semicarbazone crystallised from aqueous ethanol in needles, m. p. and mixed m. p. 138—140°.

*Catalytic Hydrogenation of the Hydrogen Sulphate of ω-Amino-*p*-methoxyacetophenone.*—The sulphate (0·7 g.) was shaken in glacial acetic acid (15 c.c.) and water (2 c.c.) with Adams catalyst (50 mg.) over hydrogen at atmospheric pressure. After absorption of about 0·66 mol. of hydrogen (*ca.* 45 min.), the rate of absorption became very slow. Fresh platinum catalyst (50 mg.) was introduced and the hydrogenation continued: it stopped after absorption of the remaining 0·34 mol. of hydrogen (*ca.* 20 min.). After filtration the clear colourless liquid was distilled under reduced pressure to remove acetic acid, and the residue treated with water and divided in two parts.

One part was condensed with *trans*-cinnamoyl chloride (0·3 c.c.) as above and the pasty mass obtained was crystallised from ethanol, giving *aegelin* as plates, m. p. and mixed m. p. 178—179° (0·15 g.) (Found: C, 72·85; H, 6·4; N, 4·5%).

The other part of the solution was condensed with β-phenylpropionyl chloride (0·3 c.c.) as before, and the solid product obtained was crystallised from ethanol, giving *dihydroaegelin* as leaflets, m. p. and mixed m. p. 140—141° (0·16 g.) (Found: C, 71·9; H, 7·1%).

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[*Received, September 20th*, 1957.]

[4] Kindler and Peschke, *Arch. Pharm.*, 1931, **269**, 581.
[5] Lister and Robinson, *J.*, 1912, **101**, 1297.

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316. *The Reactivity of Some Active Nucleophilic Reagents with Organophosphorus Anticholinesterases.*

By A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield.

Rate constants have been measured for the reaction of some hydroxamic acids and oximes with a number of organophosphorus anticholinesterases in neutral aqueous solution. The relation between dissociation constant and reactivity is examined for the above compounds and for some other active nucleophiles, including hydroxide ions.

The influence of structure on the reactivity of the organophosphorus compounds is also discussed.

During the last 20 years many organophosphorus compounds RR'P(O)X (I) have been synthesised, which, being extremely active inhibitors of the enzyme cholinesterase, are highly toxic to insect and animal life.[1] Attempts to counter the toxicity by substances which react with them under physiological conditions have only recently led to compounds with significant therapeutic effect in animals.[2] With the exception of some metal chelates,[3] the most active of these are the anions of hydroxamic acids,[4] oximes,[5] hypohalous acids,[6] and hydrogen peroxide,[7] which have in common an electronegative atom linked directly to a negatively charged oxygen atom. In an attempt to relate the reactivities of these compounds to this structural feature, we have carried out a comparative study of the reactivity of a range of compounds of this type with organophosphorus anticholinesterases (I) in which all three substituents on the phosphorus atom were varied.

Reactivity of Oximes.—In a previous paper [5] the reaction between αβ-diketone monoximes and *iso*propyl methylphosphonofluoridate (Sarin) was shown to occur by a rate-controlling attack of the oxime anion on the phosphorus compound, followed by rapid splitting of the oxime phosphonate into acidic products. Second-order rate constants were determined from the rate of acid liberation. In Table 1, these rate constants are compared with those for hydroxyiminoacetone, hydroxyiminoacetylacetone, and diacetyl monoxime, measured by colorimetric determination of the unchanged Sarin.[7b] The agreement is good and confirms the view that the rate-determining stage is the initial attack of the oxime on the Sarin. The rates obtained by the colorimetric method were slightly dependent on the nature of the buffer, those in the Table being for reaction in aqueous collidine. In phosphate buffer of the same molar concentration the rate constants were increased by about 20%. Rate constants are also given in Table 1 for the reaction of the above three oximes with other anticholinesterases in which the two groups R and R' and the leaving group X were varied independently. Both absolute and relative reactivities of the three oximes are a function of all three groups on the phosphorus atom.

Reactivity of Hydroxamic Acids.—For the reaction between Sarin and benzhydroxamic acid Swidler and Steinberg [8] have shown that the rate-determining stage is attack by the hydroxamic acid anion and is followed by rapid breakdown of the intermediate phosphorylated hydroxamic acid. Rate constants for the reaction of benzhydroxamic acid and salicylhydroxamic acid with six organophosphorus anticholinesterases are included in Table 1. That for benzhydroxamic acid with Sarin is consistent with that obtained by Swidler and Steinberg although no exact comparison can be made as the experiments were

[1] Brown, "Insect Control by Chemicals," Wiley, New York, 1951; Sartori, *Chem. Rev.*, 1951, **48**, 245; Holmstedt, *Acta Physiol. Scand.*, 1951, **25**, Suppl., 90.
[2] Epstein and Freeman, *Fed. Proc.*, 1955, **14**, 50; Askew, *Brit. J. Pharmacol.*, 1956, **11**, 417.
[3] Wagner-Jauregg, Hackley, Lies, Owens, and Proper, *J. Amer. Chem. Soc.*, 1955, **77**, 922.
[4] Hackley, Plapinger, Stolberg, and Wagner-Jauregg, *ibid.*, p. 3651.
[5] Green and Saville, *J.*, 1956, 3887.
[6] Epstein, Bauer, Saxe, and Demek, *J. Amer. Chem. Soc.*, 1956, **78**, 4068.
[7] (*a*) Epstein, Demek, and Rosenblatt, *J. Org. Chem.*, 1956, **21**, 796; (*b*) Marsh and Neale, *Chem. and Ind.*, 1956, 494.
[8] Swidler and Steinberg, *J. Amer. Chem. Soc.*, 1956, **78**, 3594.

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performed at different temperatures in different media. The rates obtained by the colorimetric method were, as for oximes, affected by the buffer, the reactivity in phosphate being greater than in collidine.

In hydroxamic acids R·CO·NH·OH (II) the substituent R is further from the acidic hydroxyl group than are the substituents R′ and R″ in oximes HO·N:CR′R″, so that steric effects of this group are likely to be less important. It seems reasonable that the affinity of

TABLE 1. *Second-order rate constants (l. mole^{-1} min.$^{-1}$) for the reaction of some oximes and hydroxamic acids at 25° with anticholinesterases* RR′P(O)X.

			Rate constant * for anion derived from					
R	R′	X	Hydroxyimino-acetylacetone pK_a ‡: 7·38	Hydroxyimino-acetone 8·30	Diacetyl monoxime 9·30	Benzhydroxamic acid 8·75	Salicylhydroxamic acid 7·43	Rate constant for hydroxide ion † —
Et	Et	F	—	(530)	—	—	—	50,000
EtO	Et	F	—	(160)	—	—	—	1200
EtO	EtO	F	18	62	—	380	33	110
Pr^{i}O	Pr^{i}O	F [a]	3·4	12	—	36	4·9	50
Pr^{i}O	Me	F [b]	73 (80)	240 (250)	380 (410)	1020	114 (130)	2000
EtO	EtO	$(EtO)_2PO_2$ [c]	35	59	16	160	19	21
EtO	EtO	$O{\cdot}C_6H_4{\cdot}NO_2$ [d]	—	0·20	0·30	1·00	0·071	0·52
EtO	Me_2N	CN [e]	95	180	60	600	90	750

[a] DFP. [b] Sarin. [c] TEPP. [d] E.600. [e] Tabun.

* The rates in parentheses were obtained by the acid-production method, while those for E.600 were obtained from the *p*-nitrophenol liberation. The rates for TEPP and those for the two oximes with DFP are for reaction in phosphate buffer; all other rates are for collidine buffer.

† The hydroxide-ion rates for DFP, E.600, and Tabun are taken from Kilpatrick and Kilpatrick (*J. Phys. Chem.*, 1949, **53**, 1371), Topley (*Chem. and Ind.*, 1950, S.859), and D. J. Marsh (personal communication). The other values were obtained from the acid production.

‡ log (reciprocal of the dissociation constant in 0·1M-KCl).

the anion for a positively charged phosphorus atom in a polarised phosphoryl group would be related to its affinity for a proton by an equation of the Brønsted or Hammett type, namely $k = c(1/K_a)^b$. The relation between log k and pK_a for the reaction of a number of hydroxamic acids with four anticholinesterases is depicted in the Figure. There is some scatter, but the relation holds moderately satisfactorily. From this type of Brønsted relation, the most reactive hydroxamic acid at any pH, including that (7·4) desired physiologically, can be readily predicted.[9]

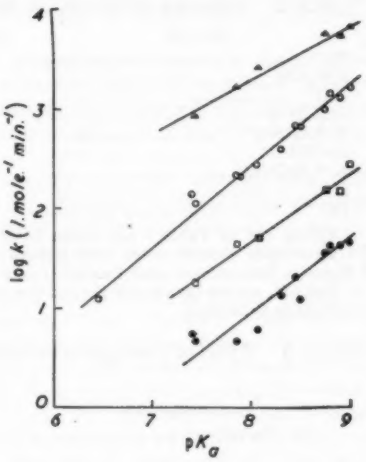
Since aldoximes [5] (III) and catechols [10] (IV) react rapidly with organophosphorus compounds, the even higher reactivity of hydroxamic acids has been attributed [8] to the hydroximic acid tautomer (V) which is related to oximes and to catechols. To decide whether the ability to adopt the hydroximic form (V) is essential, we have examined the reactivity with Sarin of *N*-hydroxyphthalimide (VI), whose anion cannot tautomerise. This compound is bright red in neutral solution so that the peroxide–dianisidine reagent could not be used, but the rate constant (5 l. mole^{-1} min.$^{-1}$) was obtained from the acid production. The pK_a of *N*-hydroxyphthalimide is 6·1 so that the above rate is not greatly below that expected from the pK_a–log k graph (Figure). It therefore seems unnecessary to invoke as an explanation that the reaction proceeds *via* the hydroximic tautomer rather than the predominant hydroxamic form.[11] The cyclic hydroxamic acids (VII) and (VIII), which also cannot adopt a hydroximic form analogous to (V), are relatively unreactive towards di*iso*propyl phosphorofluoridate (DFP),[4] but probably owing to their higher acidity.

[9] Steinberg, Swidler, and Seltzer, *Science*, 1957, **125**, 336.

[10] Jandorf, Wagner-Jauregg, O'Neill, and Stolberg, *J. Amer. Chem. Soc.*, 1951, **73**, 5202; Berry, Fellowes, Fraser, Rutland, and Todrick, *Biochem. J.*, 1955, **59**, 1.

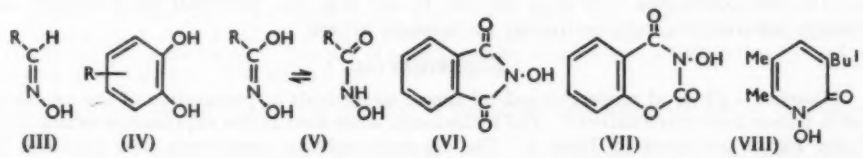
[11] Mathis, *Compt. rend.*, 1951, **232**, 505.

Discussion.—The two main factors influencing the nucleophilicity of a reagent are its electron density and polarisability, whose relative importance depends on the substrate.[12] Thus, for anions attacking a " saturated " substrate such as an alkyl halide, the repulsion between the partial negative charges on the entering and the leaving group in the transition



Reaction of hydroxamic acids at 25° in phosphate buffer with TEPP (□), and in collidine buffer with Tabun (△) (1 + log k), Sarin (○) or DFP (●). The hydroxamic acids used are listed in Table 4. pK_a = log (reciprocal of the dissociation constant in 0·1M-KCl).

state could be offset by high polarisability of the entering group. For " unsaturated " substrates such as acyl halides, this repulsion can be offset by polarisation of the substrate itself, so that polarisability is less important in the entering ion.



The mechanism of substitution in reactive phosphoryl compounds has not been established with certainty, although present evidence [13] favours direct nucleophilic replacement without the formation of an intermediate addition compound as occurs in some carbonyl substitution reactions; [14] but whether or not such intermediate formation occurs, the polarisability both of the reagent and of the phosphoryl bond appear to influence the reactivity of the phosphoryl compound with different reagents. Thus for TEPP and a single type of anion (such as those of hydroxamic acids) the rate increases with increasing basicity, but for a wider range of nucleophilic reagents the effect is less significant. On the other hand, for Sarin, basicity is much more important (cf. Table 2). It might be expected that the ability of the phosphoryl group to be polarised would decrease as conjugative substituents are attached to the phosphorus atom, in which case basicity should become less important as such substituents are added. This may explain the increased slope of the log k–pK_a curves (Figure) as the substituents on the phosphorus atom are changed from alkoxy-alkylamino to alkoxy-alkyl, and also the ratio of the reactivities of the hydroxide and the hydroxyiminoacetone ion shown in Table 3.

[12] Swain and Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 141.
[13] Dostrovsky and Halmann, *J.*, 1956, 1004.
[14] Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626.

The leaving group also has an effect on this ratio as can be seen for the diethoxyphosphoryl compounds in Table 1.

The reason for the high reactivity with organophosphorus anticholinesterases of compounds with the general structure R–Z(Y)·O⁻ remains obscure. The reactivity is far

TABLE 2. *Influence of basicity on the reactivity of nucleophiles with Sarin and TEPP.*

Reagent	pK_a *	k_{TEPP}	k_{Sarin}	k_{TEPP}/k_{Sarin}
H_2O	0	0·0017 [a]	0·0001 [b]	17
NH_2·OH	6	26 [b]	2·6	10
ClO^-	7·4	267 [b]	600 [d]	0·45
$Ac_2C{:}N{\cdot}O^-$	7·4	35	73	0·48
Ac·CH:N·O⁻	8·3	59	240	0·24
Bz·NH·O⁻	8·8	160	1020	0·16
Ac·CMe:N·O⁻	9·3	16	380	0·043
HO_3^-	11·8	2180 [b]	94,000 [b]	0·023
HO^-	14	21	2000	0·011

Values not in Table 1 are taken from: [a] Hall and Jacobson, *Ind. Eng. Chem.*, 1948, **40**, 694. [b] Unpublished results from this Laboratory. [c] Jandorf, *J. Amer. Chem. Soc.*, 1956, **78**, 3686. [d] Epstein, Bauer, Saxe, and Demek, *J. Amer. Chem. Soc.*, 1956, **78**, 4068.

* The pK_a values quoted for the oximes and hydroxamic acids are log (reciprocal of the dissociation constant in 0·1M-KCl).

TABLE 3. *Effect of conjugative substituents on the importance of basicity in phosphoryl substitution.*

Compound	$Et_2P(O)F$	EtO·PEt(O)F	$(EtO)_2P(O)F$
$k_{OH^-}/k_{Ac\cdot CH:N\cdot O^-}$	95	7·5	1·8

higher than expected from their basicity, yet is not primarily a function of polarisability since thiosulphate ions are almost unreactive with organophosphates.[7a] A feature that these anions have in common is a weak bond Z–O which breaks to give the cation $(R–Z–Y)^+$ once the oxygen atom has become attached to phosphorus. However, since this fission is not the rate-controlling step it is difficult to see how this potential bond-rupture can directly influence the rate-controlling nucleophilic attack.

EXPERIMENTAL

Materials.—Physical properties and references to methods of preparation of the oximes in Table 1 have been given earlier.[5] The hydroxamic acids used in the experiments summarised in the Figure are listed in Table 4. The organophosphorus compounds were provided by Dr. J. M. Wright of this Establishment.

TABLE 4.

Hydroxamic acid (and method)	Solvent	M. p.*	M. p. (lit.)	N (%) Calc.	N (%) Found	pK_a †
Benz- (*a*)	Ethyl acetate	127—128°	128° (*a*)	10·3	9·9	8·75
Furo- (*a*)	aq. EtOH	125—127	124 (*f*)	—	—	8·45
Glycine- (*b*)	H_2O	140—143	142—143 (*b*)	31·3	30·3	7·40
Hippuro- (*a*)	aq. EtOH	147—149	159 (*g*)	14·4	14·1	8·80
*iso*Nicotin- (*a*)	H_2O	151—153	155 (*c*)	20·3	20·1	7·85
p-Methylbenz- (*a*)	EtOH	142—144	148 (*h*)	—	—	8·90
Nicotin- (*a*)	H_2O	155—157	155 (*c*)	20·3	20·4	8·30
Nicotin- methiodide (*c*)	EtOH	177—179	187 (*c*)	—	—	6·46
m-Nitrobenz- (*a*)	aq. EtOH	140—141	151 (*i*)	15·4	15·4	8·07
Picolin- (*a*)	H_2O	119—120	120 (*c*)	20·3	20·5	8·50
Pyrimidine-2-carbox- (*a*)	H_2O	155—157	—	30·2	30·2	7·88
Salicyl- (*d*)	aq. MeOH	165	168—169 (*d*)	—	—	7·43
Tropo- (*a*)	H_2O	178—180	171—172 (*j*)	7·7	7·7	9·00
N-Hydroxyphthalimide (*e*)	aq. EtOH	225	230 (*e*)	8·6	8·5	6·10

* With decomp.; approx. † log (reciprocal of the dissociation constant in 0·1M-KCl). (*a*) Hauser and Renfrew, *Org. Synth.*, Coll. Vol. II, p. 67. (*b*) Safir and Williams, *J. Org. Chem.*, 1952, **17**, 1298. (*c*) Ref. 4. (*d*) Jeanrenaud, *Ber.*, 1889, **22**, 1273. (*e*) Lach, *Ber.*, 1883, **16**, 1781. (*f*) Pickard and Neville, *J.*, 1901, **79**, 847. (*g*) Wieland and Stimming, *Annalen*, 1953, **579**, 97. (*h*) Lossen, *ibid.*, 1895, **281**, 176. (*i*) Werner and Skiba, *Ber.*, 1899, **32**, 1662. (*j*) Steinberg and Bolger, *J. Org. Chem.*, 1956, **21**, 660.

Collidine–collidine hydrochloride buffer was prepared according to Gomori,[15] and sodium phosphate–citric acid buffer was prepared at half the concentration given by McIlvaine.[16]

Dissociation Constants.—These were determined by titration with 0·1N-sodium hydroxide of the oxime or hydroxamic acid (about 0·01M) in aqueous potassium chloride (0·1M) at 25°. The pK_a values were calculated by the Henderson–Hasselbalch equation from pH's around the half-neutralisation points. The potassium chloride was used to compensate approximately for the effect on the dissociation constants of the ionic strength of the buffers used in the kinetic experiments.

Kinetic Methods.—Three methods were used for determining the reaction rates. These were: (*a*) continuous titration with alkali of the acid produced during the reaction,[5] (*b*) colorimetric estimation of the rate of disappearance of the phosphorus compound, and (*c*) for diethyl *p*-nitrophenyl phosphate only, colorimetric measurement of the rate of liberation of *p*-nitrophenol.

Reactions (*b*) were carried out in a beaker at roughly controlled temperatures. The phosphorus compound (0·5 ml. of a 0·05M solution in "AnalaR" propan-2-ol) was added to a solution (50 ml.) of the hydroxamic acid or oxime (0·005—0·05M) in an appropriate buffer. The mixture was stirred and samples (1·0 ml.) were withdrawn at intervals and added to the peroxide–dianisidine reagent (24 ml.; see below) which was then set aside (5—30 min.) until the intensity (D_t) of the brown colour, measured on a Hilger "Spekker" photometer (601 Spectrum Violet filter), became constant. The "Spekker" readings were linearly proportional to the concentration of the phosphorus compound and were used directly in the graphical calculation of the first-order rate constants (the oxime or hydroxamic acid being in large excess) from the relation $k_{obs.} = kiA + k_{solv.} = (1/2{\cdot}303t) \log (D_0/D_t)$ where A is the concentration of the oxime or hydroxamic acid and i the fraction ionised, as calculated from the Henderson–Hasselbalch equation. The small spontaneous solvolysis rate, $k_{solv.}$, was determined independently for each organophosphate over the pH range (6·5—8) used for the reactivity measurements. A typical experiment is illustrated in Table 5. The pH of the

TABLE 5. *Reaction of* DFP *with* p-*methylbenzhydroxamic acid* (0·02M) *in collidine buffer* (pH 7·64) *at* 25°.

Time (t, min.)	0	3	6	9	12	15	18	21	25	29
"Spekker" reading (D_t)	0·628	0·551	0·468	0·416	0·368	0·311	0·272	0·237	0·194	0·161

From a graph of log D_t against t, $k_{obs.} = 0{\cdot}047$ min.$^{-1}$. At pH 7·6, $k_{solv.}$ for DFP is negligible, so that $ki = 2{\cdot}35$ l. mole^{-1} min.$^{-1}$. The pK_a of *p*-methylbenzhydroxamic acid is 8·90, so that $i = 1/\{1 +$ antilog $(pK_a - pH)\} = 0{\cdot}052$, and $k = 45$ l. mole^{-1} min.$^{-1}$.

reaction mixture was checked before addition of the phosphorus compound and at the end of the run.

The peroxide–dianisidine reagent contained the following solutions.[7b] Acetone–water buffer, 22—20 ml. of a solution containing potassium dihydrogen phosphate (8 g.) and potassium hydroxide (4·5 g.) in water (500 ml.) and acetone (500 ml.) (freed from aldehydes by contact with potassium permanganate for 1 week followed by distillation from 1% sodium hydroxide); *o*-dianisidine hydrochloride (1·0 ml. of a 1·3% aqueous solution); and 1% aqueous hydrogen peroxide (1—3 ml.).

Method (*c*): *p*-Nitrophenol in borate buffer gives an approximately linear relation between optical density [measured on a Hilger "Spekker" photometer (601 Spectrum Violet filter)] and concentration up to about 2×10^{-5}M. Above this concentration the colour intensity increased only slowly with concentration and is unsatisfactory for estimation of *p*-nitrophenol. Accordingly diethyl *p*-nitrophenyl phosphate was dissolved in an approximately half-neutralised solution of the oxime or hydroxamic acid (about 10^{-2}M) to give a concentration of at most 5×10^{-4}M. At suitable time intervals, samples (1 ml.) of this solution were diluted with 24 ml. of aqueous borax (0·05M), and the colour intensity was measured on the spectrophotometer. This dilution of the oxime or hydroxamic acid was sufficient effectively to stop the reaction. The rate constant was calculated from a graph of log $(X_\infty - X_t)$ against time, where X_t is the *p*-nitrophenol concentration at time t.

CHEMICAL DEFENCE EXPERIMENTAL ESTABLISHMENT,
PORTON DOWN, nr. SALISBURY, WILTS.

[*Received, November 6th*, 1957.]

[15] Gomori, *Proc. Soc. Exp. Biol. Med.*, 1946, **62**, 33.
[16] McIlvaine, *J. Biol. Chem.*, 1921, **49**, 183.

XUM

317. *Extrusion of Sulphur. Part III.* Polycyclic 1 : 4-Thiazepines.*

By R. H. B. Galt, J. D. Loudon, and A. D. B. Sloan.

Pyrolysis of 9-aryl-9-azidothioxanthens yields mainly anils of thioxanthones and only small amounts of 9-aryldibenzo[*b*,*f*]-1 : 4-thiazepines. Extrusion of sulphur from the thiazepine derivative (IV), obtained by condensing 1-chloroanthraquinone with *o*-aminothiophenol, yields 8-oxodibenzo-[*c*,*mn*]acridine (VII). Similarly, from the bisthiazepines prepared from 1 : 5-dichloro- and 1-chloro-4-nitro-anthraquinone, respectively, the polycyclic diaza-compounds (VIII) and (IX) are synthesised.

Dibenzo[*b*,*f*]-1 : 4-thiazepines (as I; X = S) were first prepared by Brodrick, Nicholson, and Short [1] who applied a Bischler–Napieralski type of ring-closure to 2-benzamidodiaryl sulphides. A different route was taken by Jarrett and Loudon (Part II) who condensed *o*-aminothiophenol with reactive *o*-chlorophenyl-aldehydes or -ketones. We have now extended this method to include reagents of the chloroanthraquinone type and have also examined expansion of the central ring of thioxanthhydrols.

9-Arylxanthhydrols (as II; X = O) and 9-arylthioxanthhydrols (as II; X = S) are readily accessible [2,3] and transformation of the derived azides offers a possible route to dibenzoxazepines (as I; X = O) and dibenzothiazepines (as I; X = S), respectively. By analogy with triphenylmethyl azide [4] such azides should be stable towards mineral acids and, indeed, they were conveniently prepared by adding sodium azide to a solution of the appropriate xanthylium or thioxanthylium sulphate in sulphuric acid. The Schmidt reaction is consequently inoperative although it may be noted that by this means, and presumably under the driving force of central-ring aromatisation, 9-phenylfluoren-9-ol is converted in high yield into 9-phenylphenanthridine.[5] On the other hand pyrolysis of triphenylmethyl azide yields benzophenone anil [6] and we now find that azides derived from carbinols of type (II; X = O or S) are transformed by heat into mixtures of the compounds (I; X = O or S) and (III; X = O or S). Since, however, in these mixtures anils (III) usually predominate and require wasteful separation, the method does not provide an attractive synthesis of oxazepine and thiazepine derivatives.

Condensation of *o*-aminothiophenol with 1-chloroanthraquinone in presence of alkali should yield 1-(*o*-aminophenylthio)anthraquinone. However the immediate product proved to be susceptible to dehydration and it was therefore directly converted by boiling acetic acid into the thiazepine (IV; R = R′ = H). Similarly 1 : 5-dichloroanthraquinone yielded the compound (IV; R = Cl, R′ = H) and, either thence or directly, with a further mol. of *o*-aminothiophenol furnished the bisthiazepine (V). By the same procedure 1-chloro-4-nitroanthraquinone afforded first the chloro-thiazepine (IV; R = H, R′ = Cl) —the nitro-group rather surprisingly being replaced in preference to the chloro-substituent —and then the bisthiazepine (VI).

Brodrick *et al.*[1] report the conversion of 2 : 8-dibromo- and of 2 : 8-dicyano-11-phenyldibenzo[*b*,*f*]-1 : 4-thiazepine into corresponding phenanthridines by cuprous salts in boiling quinoline. The yields were poor and similar extrusion of sulphur from the parent compound (I; X = S) was not detected. We now find that this compound (I; X = S) when

* Part II, *J.*, 1957, 3818.

[1] Brodrick, Nicholson, and Short, *J.*, 1954, 3857. We thank Dr. C. I. Brodrick for drawing our attention to this paper which regrettably we had overlooked: in it dibenzo[*b*,*f*]-1 : 4-thiazepines are named as 2 : 3-6 : 7-dibenzo-1-thia-4-aza*cyclo*hepta-2 : 4 : 6-trienes.

[2] Loudon, Robertson, and Watson, *J.*, 1950, 55.

[3] Campbell, Dick, Ferguson, and Loudon, *J.*, 1941, 747.

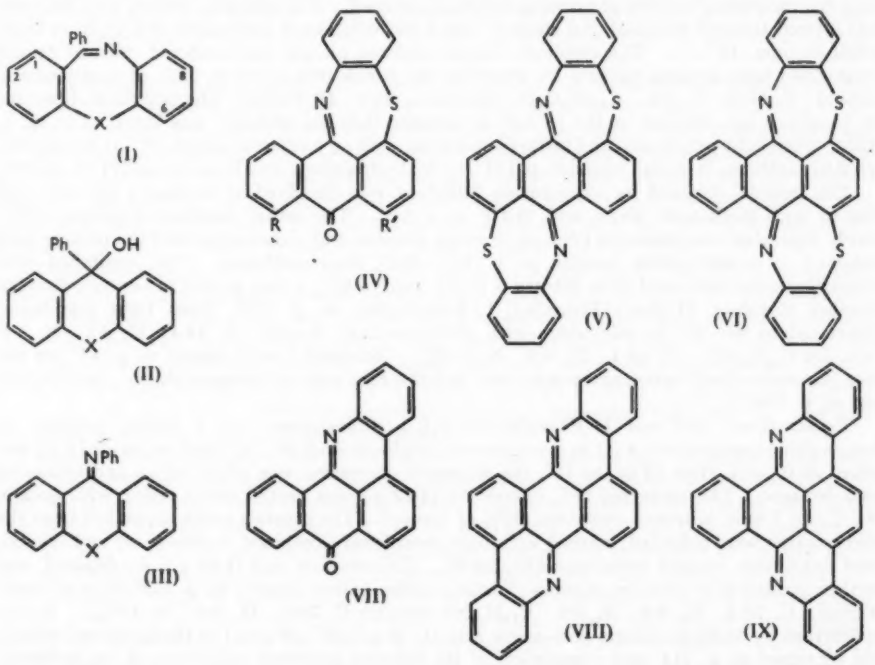
[4] Wieland, *Ber.*, 1909, **42**, 3020; Arcus and Mesley, *J.*, 1953, 178; Newman and Hay, *J. Amer. Chem. Soc.*, 1953, **75**, 2322.

[5] Arcus and Coombs, *J.*, 1954, 4319.

[6] Senior, *J. Amer. Chem. Soc.*, 1916, **38**, 2718.

heated with copper in diethyl phthalate (cf. Part II) affords 9-phenylphenanthridine in over 90% yield. Under the same conditions the thiazepine (IV; R = R′ = H) yielded 8-oxodibenz[*c*,*mn*]acridine (VII) and the bisthiazepines (V) and (VI) gave the polycyclic diaza-compounds, (VIII) and (IX), respectively, all in high yield. On the other hand the chloro-compounds (IV; R = Cl, R′ = H) and (IV; R = H, R′ = Cl) gave ill-defined products from which no pure compound was isolated. The dibenzacridine (VII) and 8 : 16-diazadibenzo[*b*,*k*]perylene (VIII) had the properties recorded by Braude and Fawcett [7] who synthesised these compounds *via* the adducts of *o*-nitrophenylbutadiene with naphthaquinone and benzoquinone, respectively. The ultraviolet absorption spectrum of the hitherto unknown 11 : 16-diazatribenzo[*a*,*e*,*i*]pyrene (IX) resembles that of its carbocyclic analogue.[8]

At least in favourable cases extrusion of sulphur from thiazepines in boiling diethyl phthalate appears to be largely a thermal decomposition, only slightly better yields being obtained in presence of copper. Thus the thiazepine (IV; R = R′ = H) gave the acridine



(VII) in 71% yield in this solvent alone, in 75% yield in presence of hydrogen-free Raney nickel, and in 83% yield in presence of copper bronze. The Raney nickel catalyst in boiling xylene [9] was ineffective, as was simple heating in phosphoryl chloride, in phosphoryl chloride–dimethylformamide,[10] or in acetic acid. Heating the thiazepine in acetic acid with hydrogen peroxide gave the acridine (VII) in 67% yield. This is the third type of product to be obtained from 11-aryldibenzothiazepines with this reagent which, in other cases, has oxidised the thiazepine to the *S*-dioxide [1] or broken the heterocycle as in the formation of 2-benzoyl-2′ : 4-dinitrodiphenyl sulphone from the 2-nitro-derivative of

[7] Braude and Fawcett, *J.*, 1951, 3117; cf. Koelsch, *J. Amer. Chem. Soc.*, 1936, **58**, 1325.
[8] Clar, *J.*, 1949, 2168.
[9] Hauptmann and Wladislaw, *J. Amer. Chem. Soc.*, 1950, **72**, 707, 711.
[10] Parham and Traynelis, *ibid.*, 1954, **76**, 4960.

compound (I; X = S) (Part II). It recalls the ring-contraction to thiophens accompanying similar oxidation of *p*-dithiins.[10] Moreover in the present instance some hydrogen sulphide was evolved and this may suggest the elimination of sulphur monoxide from an intermediate thiazepine *S*-monoxide, followed by the disproportionation: $3SO + H_2O \longrightarrow 2SO_2 + H_2S$.

Experimental

Light petroleum refers to the fraction of b. p. 60—80°.

9-Azido-9-phenylxanthen, m. p. 110° (from light petroleum), was obtained almost quantitatively when a solution of sodium azide (10 g.) in water (40 c.c.) was added (7 min.) to a cold solution of 9-phenylxanthhydrol (5·0 g.) in sulphuric acid (50 c.c.)–water (100 c.c.) (Found: C, 76·1; H, 4·1; N, 13·9. $C_{19}H_{13}ON_3$ requires C, 76·2; H, 4·4; N, 14·0%). When heated for a few min. in ethanol it afforded 9-ethoxy-9-phenylxanthen, m. p. and mixed m. p. 103°.[11]

Xanthone Anil and 11-*Phenyldibenz*[b,f]-1 : 4-*oxazepine*.—A solution of the preceding azide (1 g.) in decalin (2 c.c.; distilled from sodium) was heated under reflux for 20 min. by which time the theoretical volume of nitrogen had been evolved. The solution, diluted with benzene, was filtered through charcoal and treated with a hot solution of picric acid (0·4 g.) in benzene (total volume, 15 c.c.). The resultant orange-coloured picrate was collected (filtrate-*A*) and crystallised from benzene (filtrate-*B*), affording the *picrate* (0·4 g.), m. p. 227°, of xanthone anil (Found: C, 60·3; H, 3·5. $C_{25}H_{16}O_8N_4$ requires C, 60·0; H, 3·2%). The anil itself, liberated by passing a hot solution of the picrate in benzene through alumina, was identical in m. p. (135°; from light petroleum) and infrared spectrum with an authentic sample.[12] It was hydrolysed to xanthone, m. p. and mixed m. p. 174°, by 5N-hydrochloric acid in acetic acid (1 : 1) at 100°.

The residue obtained by evaporating filtrate-*A* was dissolved in methanol (10 c.c.) and treated with methanolic picric acid (0·4 g. in 5 c.c.). The rather discoloured picrate which slowly separated was passed in benzene through alumina and reconverted into the picrate, now obtained as canary-yellow needles, m. p. 150—152°, from methanol. This, combined with similar material recovered from filtrate-*B* (total yield, 0·92 g.), was passed in benzene through alumina affording 11-phenyldibenz[*b*,*f*]-1 : 4-oxazepine, m. p. 108° (from light petroleum) (depressed to 90—97° by admixture with xanthone anil) (Found: C, 84·4; H, 4·8; N, 5·1. Calc. for $C_{19}H_{13}ON$: C, 84·1; H, 4·8; N, 5·2%). Brodrick *et al.*[13] record m. p. 81° for the base (for which their carbon analysis is poor) and this may indicate polymorphism: their picrate had m. p. 150°.

Thioxanthone Anil and 11-*Phenyldibenzo*[b,f]-1 : 4-*thiazepine*.—To a stirred solution of 9-phenylthioxanthhydrol (4 g.) in concentrated sulphuric acid (10 c.c.), sodium azide (4 g.) was added at 0° and, after 12 hr. at 18°, the resultant suspension was added to ice and extracted with benzene. The recovered red, viscous oil (4·13 g.) was heated under reflux with decalin (8 c.c.) for 7 min. (nitrogen-evolution, 95% of theory). The crystals which separated from the cold solution were collected, washed with light petroleum (combined in filtrate-*A*) and crystallised twice from ethanol (combined filtrates-*B*). *Thioxanthone anil* (1·81 g.), so obtained, was further purified in benzene on alumina affording golden-yellow needles, m. p. 153° (from ethanol) (Found: C, 79·5; H, 4·9; N, 5·0. $C_{19}H_{13}NS$ requires C, 79·4; H, 4·6; N, 4·9%). It was hydrolysed by 5N-hydrochloric acid–acetic acid (1 : 2) at 100° (30 min.) to thioxanthone, identified by mixed m. p. 214° and comparison of its infrared spectrum with that of an authentic sample.[14]

The residue obtained by evaporating filtrates-*B* was added to filtrate-*A* and the whole was extracted with 5N-hydrochloric acid (5 × 20 c.c.). The extract was heated at 100° (1 hr.), cooled, and filtered from thioxanthone (0·75 g.), and the filtrate concentrated at 100° *in vacuo*. Aqueous sodium carbonate was then added and a benzene extract, after chromatography on alumina, afforded 11-phenyldibenzo[*b*,*f*]-1 : 4-thiazepine (0·52 g.), m. p. 117° (from methanol) (Found: C, 79·7; H, 4·4; N, 5·0. Calc. for $C_{19}H_{13}NS$: C, 79·4; H, 4·6; N, 4·9%): Brodrick *et al.*[1] give m. p. 117—118°.

3′ : 5-Dinitro-2-(phenylthio)benzophenone.—To a hot stirred suspension of 2-chloro-3′ : 5-dinitrobenzophenone (1 g.) in ethanol–water (2 : 1; 7·5 c.c.) a solution of thiophenol (0·5 g.) and

[11] Büntzly and Decker, *Ber.*, 1904, **37**, 2931.
[12] Schönberg and Asker, *J.*, 1942, 725; Graebe and Röder, *Ber.*, 1899, **32**, 1688.
[13] Brodrick, Donaldson, Nicholson, Short, and Wibberley, *J.*, 1953, 1079.
[14] Gomberg and Britton, *J. Amer. Chem. Soc.*, 1921, **43**, 1945.

sodium hydroxide in the same solvent (6 c.c.) was added portionwise during 65 min. After each addition the mixture was heated under reflux and heating was continued finally for 15 min. 3′ : 5-*Dinitro*-2-(*phenylthio*)*benzophenone* formed pale yellow needles, m. p. 124° (from ethanol) (Found: C, 60·2; H, 3·4. $C_{19}H_{12}O_5N_2S$ requires C, 60·0; H, 3·2%).

2-*Nitrothioxanthone* m-*Nitroanil and* 2-*Nitro*-11-m-*nitrophenyldibenzo*[b,f]-1 : 4-*thiazepine*.—To an ice-cooled solution of 3′ : 5-dinitro-2-(phenylthio)benzophenone (0·5 g.) in concentrated sulphuric acid (2 c.c.) sodium azide (0·5 g.) was added and, after 12 hr., the mixture was poured on ice. The resultant precipitate was washed with water, aqueous sodium carbonate, and then water, dried *in vacuo*, and extracted with boiling benzene (charcoal). Addition of light petroleum to the concentrated extract gave a crystalline azide (0·4 g.; m. p. 147°) which was heated (7 min.) with decalin (5 c.c.) under reflux. The solid obtained from the cooled solution was crystallised from benzene (charcoal) affording, as the first crop (filtrate-*A*), yellow needles (0·176 g.) of 2-*nitrothioxanthone* m-*nitroanil*, m. p. 259° (Found: C, 60·5; H, 2·9; N, 11·3. $C_{19}H_{11}O_4N_3S$ requires C, 60·5; H, 2·9; N, 11·1%). When hydrolysed by acid, it gave 2-nitrothioxanthone identical in m. p. 225—227° and in infrared spectrum with an authentic sample.[15]

A second crop of crystals, obtained from filtrate-*A*, was chromatographed in benzene on alumina and afforded in the first eluate 2-nitro-11-*m*-nitrophenyldibenzo[*b*,*f*]-1 : 4-thiazepine (0·013 g.) identified by m. p. 274—278° and infrared spectrum with an authentic sample (Part II).

2-*Nitro*-9-*phenylthioxanthhydrol*.—To a refluxing solution of 2-chloro-5-nitrobenzophenone (1·3 g.) and thiophenol (0·55 g.) in ethanol (17 c.c.) and water (5 c.c.) there was added a hot solution of sodium hydroxide (0·27 g.) in ethanol–water (1 : 1; 10 c.c.) and then ethanol (10 c.c.). Heating was continued for 1 hr., then the oil, which formed in the cooled mixture, was separated, taken into ether, the ethereal solution washed with water and dried, and the product recovered and dissolved in concentrated sulphuric acid. After 12 hr. the red solution was poured into ice–water, affording 2-*nitro*-9-*phenylthioxanthhydrol*, m. p. 155° (from benzene–light petroleum) (Found: C, 68·3; H, 4·1. $C_{19}H_{13}O_3NS$ requires C, 68·1; H, 3·9%).

2-*Nitrothioxanthone Anil*.—A solution of the foregoing xanthhydrol (0·5 g.) in concentrated sulphuric acid (1 c.c.) was treated with sodium azide (0·5 g.) and, after 12 hr., the whole was added to ice-water. The precipitate was dried and crystallised from benzene–light petroleum (1 : 4). The resultant azide (0·42 g.; m. p. 120°) was decomposed (7 min.) in boiling decalin (1 c.c.) from which after cooling 2-*nitrothioxanthone anil*, m. p. 205° (from benzene), was obtained in 86% yield (based on the azide) (Found: C, 68·75; H, 3·5; N, 8·75. $C_{19}H_{12}O_2N_2S$ requires C, 68·7; H, 3·6; N, 8·4%). Although probably present, no thiazepine was detected. The anil was identified by hydrolysis to 2-nitrothioxanthone.

2-*Methyl*-7-*nitrothioxanthone Anil*.—Essentially as described for the foregoing compound, 5-nitro-2-*p*-tolylthiobenzophenone in concentrated sulphuric acid was converted into an azide which by decomposition in decalin yielded 2-*methyl*-7-*nitrothioxanthone anil*, m. p. 200—202° (from benzene), in 74% yield (Found: C, 69·7; H, 4·2; N, 8·65. $C_{20}H_{14}O_2N_2S$ requires C, 69·4; H, 4·1; N, 8·1%). Again no thiazepine was detected and hydrolysis of the anil gave 2-methyl-7-nitrothioxanthone which was identified by m. p. 264° [3] and infrared spectrum.

9-*Oxoanthra*[9,1-ef]*benzo*[b]*thiazepine* (IV; R = R′ = H).—To a solution of 1-chloroanthraquinone (0·22 g.) in peroxide-free dioxan (4 c.c.) were added *o*-aminothiophenol hydrochloride (0·18 g.) and then, dropwise, a solution of sodium hydroxide (0·1 g.) in ethanol–water (1 : 1; 2 c.c.). The whole was heated at 100° for 30 min., then cooled and water added. An acetic acid solution of the resultant red solid was heated under reflux for 1 hr., affording the thiazepine (IV; R = R′ = H) as yellow needles (0·2 g.), m. p. 218° (from acetic acid) (Found: C, 76·35; H, 4·05. $C_{20}H_{11}ONS$ requires C, 76·7; H, 3·55%).

10-*Chloro*-9-*oxoanthra*[9,1-ef]*benzo*[b]*thiazepine* (IV; R = Cl, R′ = H).—1 : 5-Dichloroanthraquinone (0·35 g.) in dioxan (8 c.c.) was treated as for the 1-chloro-compound (but for 3 hr.) with sodium *o*-aminophenyl sulphide (1 mol.) generated as before. The immediate product, after being heated (2 hr.) in acetic acid, gave an insoluble yellow solid (0·05 g., m. p. >360°; cf. below) and the more soluble *thiazepine* (IV; R = Cl, R′ = H) as orange-red needles (0·29 g.), m. p. 239° (from acetic acid) (Found: C, 68·7; H, 2·85; N, 4·4. $C_{20}H_{10}ONSCl$ requires C, 69·1; H, 2·7; N, 4·0%).

Anthra[9,1-ef, 10,5-e′f′]*bisbenzo*[b]*thiazepine* (V).—When two mols. of sodium *o*-aminophenyl sulphide were used in the preceding reaction, or when the thiazepine (IV; R = Cl, R′ = H)

[15] Mayer, *Ber.*, 1909, **42**, 3046.

was treated with one mol. of this reagent, the procedure described gave the yellow solid (m. p. >360°) in *ca.* 75% yield. This afforded the *bisthiazepine* (V) as yellow needles from ethylene glycol (Found: C, 74·3; H, 3·7; N, 6·8. $C_{26}H_{14}N_2S_2$ requires C, 74·6; H, 3·4; N, 6·7%).

8-*Chloro*-9-*oxoanthra*[9,1-ef]*benzo*[b]*thiazepine* (IV; R = H, R′ = Cl) *and Anthra*[9,1-ef, 10,4-e′f′]*bisbenzo*[b]*thiazepine* (VI).—By the procedures described above 1-chloro-4-nitroanthraquinone was converted into the *monothiazepine* (IV; R = H, R′ = Cl), m. p. 229° (from acetic acid), in 50% yield (Found: C, 68·9; H, 3·0; N, 4·6%), and the *bisthiazepine* (VI), m. p. 262° (from acetic acid), in 51% yield (Found: C, 74·4; H, 3·2; N, 6·9%).

9-*Phenylphenanthridine*.—11-Phenyldibenzothiazepine (0·15 g.), copper bronze (0·15 g.), and diethyl phthalate (1 c.c.) were heated (65 min.) under reflux in an atmosphere of nitrogen. The mixture was diluted with benzene and filtered (warm) through charcoal. A hot solution of picric acid (0·15 g.) in benzene was added to the filtrate and 9-phenylphenanthridine picrate (0·24 g., 94% yield), m. p. 250—252°, collected: Arcus and Coombs [5] record m. p. 251°. The base, liberated from the picrate, was identical in m. p. 105° and infrared spectrum with an authentic sample[16] (Found: C, 89·1; H, 5·05; N, 5·6. Calc. for $C_{19}H_{13}N$: C, 89·4; H, 5·1; N, 5·5%). After a reaction time of 7 min. the base was isolated (by fractional crystallisation from admixture with the thiazepine) in 33% yield; and after 20 min. the picrate was obtained in 80% yield.

8-*Oxodibenzo*[c,mn]*acridine* (VII).—(*a*) A solution of the thiazepine (IV; R = R′ = H) (0·3 g.) in diethyl phthalate (4 c.c.) was boiled under nitrogen with copper bronze for 5—7 min. The cooled mixture was diluted with benzene, heated with charcoal, filtered, and concentrated, affording the acridine [7] (0·22 g.), m. p. 224° (from acetic acid); $\lambda_{max.}$ 363 (shoulder), 303, 382 mμ (log ε 4·465, 4·19 and 4·15) in chloroform (Found: C, 85·1; H, 3·9; N, 5·3. Calc. for $C_{20}H_{11}ON$: C, 85·4; H, 3·9; N, 5·0%).

(*b*) A solution of the thiazepine (0·2 g.) in acetic acid (25 c.c.) containing hydrogen peroxide (30%; 0·6 c.c.) was heated under reflux for 45 min., during which hydrogen sulphide was evolved. The solution was concentrated, the residue treated with water, and the resultant solid chromatographed on alumina in benzene–light petroleum (2 : 1) affording the acridine in 67% yield.

8 : 16-*Diazadibenzo*[b,k]*perylene* (VIII).—This compound, m. p. ~370°, was obtained in 78% yield when procedure (*a*) was applied to the bisthiazepine (V) and the solid product was recovered in chloroform from a Soxhlet thimble (Found: C, 88·2; H, 3·9; N, 7·95. Calc. for $C_{26}H_{14}N_2$: C, 88·1; H, 4·0; N, 7·9%); $\lambda_{max.}$ 258 (shoulder), 273 (sh), 282, 294, 370, 390, 410, and 435 mμ (log ε 4·38, 4·47, 4·57, 4·68, 4·15, 4·33, 4·59, and 4·65) in dioxan.[7]

11 : 16-*Diazatribenzo*[a,e,i]*pyrene* (IX).—This compound, m. p. 311° (from xylene), was similarly obtained in 76% yield from the bisthiazepine (VI) (Found: C, 87·9; H, 3·7; N, 7·9. $C_{26}H_{14}N_2$ requires C, 88·1; H, 4·0; N, 7·9%); $\lambda_{max.}$ 267, 283, 292, 323, 368, 382, 388, and 408 mμ (log ε 4·67, 4·71, 4·86, 4·17, 4·39, 4·37, 4·38, and 3·90) in dioxan.

We thank the Department of Scientific and Industrial Research for a Maintenance Allowance (to R. H. B. G.) and the University of Glasgow for the award of the J. and P. Coats Fellowship (to A. D. B. S.). Microanalyses were by Mr. J. M. L. Cameron and his staff.

THE UNIVERSITY, GLASGOW, W.2. [*Received, November 13th,* 1957.]

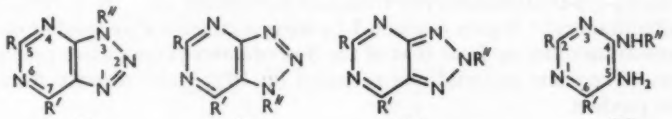
[16] Morgan and Walls, *J.*, 1931, 2447; Walls, *J.*, 1945, 294.

318. *The Synthesis of the* v-*Triazolo*[d]*pyrimidine Analogues of Adenosine, Inosine, Guanosine, and Xanthosine, and a New Synthesis of Guanosine.*

By J. Davoll.

The synthesis is described of the compounds named in the title, and of other glycosyl-*v*-triazolo[*d*]pyrimidines, from chloromercuri-derivatives of appropriate triazolopyrimidines. A new synthesis of guanosine (from 2-methylthio-9-β-D-ribofuranosyladenine) has been accomplished.

Derivatives of *v*-triazolo[*d*]pyrimidine, particularly the 5-amino-7-hydroxy-compound ("8-azaguanine") (I; R = NH_2, R′ = OH, R″ = H) have attracted considerable attention as purine antagonists in biological systems, including viruses [1] and cancers.[2] Since these compounds appear to function by incorporation as ribosyl derivatives, the synthesis, for biological testing, of derivatives analogous to the natural purine nucleosides was undertaken.



(I) (II) (III) (IV)

Two synthetic routes were used. The first of these, treatment of 5-amino-4-glycosylaminopyrimidines (IV) with nitrous acid, like the analogous syntheses of purine nucleosides by Todd and his co-workers,[3] defines the point of attachment of the sugar to the base but is of little preparative value for furanose derivatives. This method was used to prepare 7-amino-3-β-D-glucopyranosyl-*v*-triazolo[*d*]pyrimidine (I; R = H, R′ = NH_2, R″ = β-D-glucopyranosyl) from the glucosylaminopyrimidine [4] (IV; R = MeS, R′ = NH_2, R″ = D-glucosyl) by cyclisation and desulphurisation.

The second synthetic method involved the reaction of chloromercuri-derivatives of appropriate *v*-triazolo[*d*]pyrimidines with acylglycosyl halides; in the purine series this route affords the natural purine nucleosides in moderate yield.[5] A disadvantage is that two isomers (II) and (III) may be formed in addition to the required analogue (I), and in one case three products were in fact obtained. Since no unambiguous syntheses of 1- or 2-alkyl-*v*-triazolo[*d*]pyrimidines for spectroscopic comparison were available, structures could not be assigned with certainty to some of the compounds obtained.

The required *v*-triazolo[*d*]pyrimidines were prepared by standard methods (modified in some cases to avoid isolation of intermediates), acetylated, and converted into chloromercuri-compounds as described for the corresponding purines.[5,6] These were condensed with acylglycosyl halides in the usual way,[5,6] the ribofuranosyl derivatives being prepared from tri-*O*-benzoyl-D-ribofuranosyl chloride with the modifications introduced by Kissman *et al.*[7]

Deacetylation of the condensation product of 7-acetamido-*x*-chloromercuri-*v*-triazolo[*d*]-pyrimidine with tetra-*O*-acetyl-D-glucosyl bromide gave 7-amino-3-β-D-glucopyranosyl-*v*-triazolo[*d*]pyrimidine, identical with material obtained by the first route, together with an

[1] Matthews and Smith, "Advances in Virus Research," Academic Press, New York, 1955, Vol. III, p. 49.
[2] Parks, "Antimetabolites and Cancer," Amer. Assoc. Advancement Science, Washington, D.C., 1955, p. 175.
[3] Kenner, Taylor, and Todd, *J.*, 1949, 1620, and other papers in this series.
[4] Holland, Lythgoe, and Todd, *J.*, 1948, 965.
[5] Davoll and Lowy, *J. Amer. Chem. Soc.*, 1951, **73**, 1650.
[6] *Idem, ibid.*, 1952, **74**, 1563.
[7] Kissman, Pidacks, and Baker, *ibid.*, 1955, **77**, 18.

isomeric compound. On the basis of a comparison of the ultraviolet spectrum of the latter compound with the 3-isomer, and with 7- and 9-methyladenine, this is considered to be the 1-glucopyranosyl derivative (II; R = H, R′ = NH_2, R″ = β-D-glucopyranosyl), but the alternative (III) cannot be definitely excluded. A similar condensation with use of tri-*O*-benzoyl-D-ribofuranosyl chloride gave only one crystalline product; this is the required 3-β-D-ribofuranosyl derivative (" 8-aza-adenosine ") (I; R = H, R′ = NH_2, R″ = β-D-ribofuranosyl) since its spectrum is virtually identical with that of the 3-glucopyranosyl derivative. On deamination it gave the 7-hydroxy-compound (" 8-azainosine ") (I; R = H, R′ = OH; R″ = β-D-ribofuranosyl).

The preparation of the triazolopyrimidine analogue of guanosine proved more difficult. In an attempt to apply the method used for the synthesis of guanosine [5] 5 : 7-diacetamido-*x*-chloromercuri-*v*-triazolo[*d*]pyrimidine was condensed with tri-*O*-benzoyl-D-ribofuranosyl chloride and the product deacylated. The resulting crystalline compound had an indefinite melting point and a comparison of its spectrum with that of 5 : 7-diamino-3-methyl-*v*-triazolo[*d*]pyrimidine did not give any definite information as to structure. Conversion into a guanine analogue [5] gave (in 24% yield) a single product, possibly 5-amino-7-hydroxy-1-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (II; R = NH_2, R′ = OH, R″ = β-D-ribofuranosyl); it gave 5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine on hydrolysis and had a spectrum differing from that of the 3-ribofuranosyl derivative prepared as described below. The same material was prepared (in 16% yield) directly from the crude condensation product.

The successful preparation [8] of N^2-alkylguanines from 2-methylthiohypoxanthine suggested an alternative route to the required compound, and in a model experiment 2-methylthio-9-β-D-ribofuranosylhypoxanthine (prepared from the adenine derivative [6]) gave a 24% yield of guanosine, identical with the natural nucleoside, on treatment with aqueous-ethanolic ammonia at 130°. When this route was applied in the triazolopyrimidine series two isomeric ribofuranosyl derivatives of 7-amino-5-methylthio-*v*-triazolo[*d*]pyrimidine were obtained. One of these was shown to be the required 3-β-D-ribofuranosyl derivative (I; R = MeS, R′ = NH_2, R″ = β-D-ribofuranosyl) by desulphurisation, and the other compound is provisionally assumed to be the 1-β-D-ribofuranosyl derivative (II). Both compounds were deaminated with nitrous acid, and the resulting 7-hydroxy-derivatives were heated with aqueous-ethanolic ammonia. No crystalline riboside was isolated from the second compound, but the 3-β-D-ribofuranosyl derivative gave the required 5-amino-7-hydroxy-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (" 8-azaguanosine ") (I; R = NH_2, R′ = OH, R″ = β-D-ribofuranosyl), spectroscopically identical with the biosynthetic product.[9] The yield (8%) on the amination, however, was much lower than in the purine series, and a more satisfactory preparative method was sought.

It has been recently shown [10] that the chloromercuri-route may give *N*-glycosyl derivatives even in compounds where lactam–lactim tautomerism is possible, and it was found that deacylation of the condensation product of 5-acetamido-*x*-chloromercuri-7-hydroxy-*v*-triazolo[*d*]pyrimidine with tri-*O*-benzoyl-D-ribofuranosyl chloride in fact gave the required analogue of guanosine in 39% yield, together with an approximately equal amount of an isomeric compound which differed also from the (?) 1-ribofuranosyl derivative described above; it is tentatively regarded as 5-amino-7-hydroxy-2-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (III; R = NH_2, R′ = OH, R″ = β-D-ribofuranosyl).

5 : 7-Dihydroxy-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (" 8-azaxanthosine ") (I; R = R′ = OH; R″ = β-D-ribofuranosyl) was prepared by deamination of the above guanosine analogue.

Some spectral characteristics of our products are given in the annexed Table.

[8] Elion, Lange, and Hitchings, *J. Amer. Chem. Soc.*, 1956, **78**, 217.
[9] Friedkin, *J. Biol. Chem.*, 1954, **209**, 295.
[10] Fox, Yung, Davoll, and Brown, *J. Amer. Chem. Soc.*, 1956, **78**, 2117.

XUM

v-Triazolo[d]pyrimidine deriv.	$\lambda_{max.}$ (mμ) ($10^{-3}\varepsilon$ in parentheses) In HCl	At pH 6·8	In NaOH
(?) 7-Amino-1-β-D-glucopyranosyl-	244 (5·3), 286 (11·6) [a]	246 (5·5), 299 (10·3)	245 (5·3), 299 (9·8) [a]
7-Amino-3-β-D-glucopyranosyl-	263 (12·5) [a]	280 (11·7)	280 (11·2) [a]
7-Amino-3-β-D-ribofuranosyl-	260 (12·4) [a]	279 (12·0)	278 (12·4) [a]
7-Hydroxy-3-β-D-ribofuranosyl-	255 (9·4) [a]	256 (8·8)	277 (10·5) [a]
(?) 5 : 7-Diamino-β-D-ribofuranosyl-	260 (11·5), 286 (10·0) [a]	222 (21·7), 291 (7·2)	293 (7·4) [a]
5 : 7-Diamino-3-methyl-	254 (9·1), 284 (6·7) [a]	258 (5·1), 287 (8·8)	259 (5·1), 287 (8·8) [a]
(?) 7-Amino-5-methylthio-1-β-D-ribofuranosyl-	230 (12·3), 285 (13·3), 303 (12·6) [b]	223 (15·9), 248 (13·3), 279 (10·5), 308 (9·8)	248 (14·4), 279 (10·3), 310 (10·1) [b]
7-Amino-5-methylthio-3-β-D-ribofuranosyl-	245 (13·7), 280 (14·7) [b]	248 (19·4), 289 (13·5)	247 (18·9), 289 (12·9) [b]
(?) 7-Hydroxy-5-methylthio-1-β-D-ribofuranosyl-	222 (14·0), 238 (14·8), 287 (9·9) [b]	219 (15·0), 242 (14·3), 288 (9·8)	244 (15·0), 276 (9·8), 300 (10·8) [b]
7-Hydroxy-5-methylthio-3-β-D-ribofuranosyl-	232 (9·5), 273 (18·0) [b]	242 (12·5), 276 (15·1)	242 (16·8), 283 (14·8) [b]
(?) 5-Amino-7-hydroxy-1-β-D-ribofuranosyl-	285 (6·3) [c]	238 (sh) (8·4), 297 (7·1)	254 (5·6), 256 (5·6), 304 (8·8) [d]
(?) 5-Amino-7-hydroxy-2-β-D-ribofuranosyl-	238 (sh) (7·5), 296 (4·7) [c]	237 (sh) (8·4), 301 (5·6) [c]	303 (6·3) [d]
5-Amino-7-hydroxy-3-β-D-ribo-ribofuranosyl- [f]	255 (13·6), 269 (sh) (10·3) [c]	—	221 (23·0), 279 (11·6) [d]
,, ,, [g]	256 (13·7), 275 (sh) (9·5) [c]	256 (13·7), 275 (sh) (9·5)	222 (24·6), 279 (11·9) [d]
,, ,, [h]	254 (12·9), 270 (sh) [c]	256 (10·9), 270 (sh)	277 (11·2) [d]
5 : 7-Dihydroxy-3-β-D-ribofuranosyl-	240 (sh) (5·9), 256 (9·5) [a]	252 (9·7), 277 (8·8)	251 (7·1), 280 (9·5) [a]
2-Methylthio-9-β-D-ribofuranosylhypoxanthine	265 (15·1) [b]	262 (14·8)	225 (19·2), 271 (14·8) [b]

[a] 0·1N. [b] 0·05N. [c] 0·01N. [d] 0·03N. [e] In H_2O. [f] From 5-methylthio-compound. [g] From 5-acetamido-7-hydroxy-*v*-triazolo[*d*]pyrimidine. [h] Biosynthetic (ref. 9). [i] pH 7·5.

Experimental

7-Amino-3-β-D-glucopyranosyl-v-triazolo[d]*pyrimidine.*—An aqueous solution (200 c.c.) of 5 : 6-diamino-4-D-glucosylamino-2-methylthiopyrimidine, prepared [4] from 6-amino-4-D-glucosylamino-2-methylthiopyrimidine (6·5 g.), was treated with glacial acetic acid (22 c.c.), followed by sodium nitrite (1·43 g.) in water (20 c.c.), added dropwise with stirring. After 2 hr. at room temperature, the solution was evaporated to dryness below 40°, the residue acetylated with acetic anhydride–pyridine at room temperature, and the product (3·64 g.) isolated with chloroform as an amorphous powder. A solution of this material in ethanol (250 c.c.) was boiled under reflux for 2 hr. with Raney nickel [11] (from 28 g. of alloy) and filtered hot. The residue (1·77 g.) obtained by evaporation of the combined filtrate and washings was deacetylated with methanolic ammonia at 0°, and the product converted into the *picrate* (1·41 g., 13% overall yield), plates, m. p. 187—191° (decomp.), raised to 201° (decomp.) by four recrystallisations from water (Found: C, 35·9; H, 3·4; N, 23·8. $C_{10}H_{14}O_5N_6,C_6H_3O_7N_3$ requires C, 36·4; H, 3·3; N, 23·9%).

Treatment of the picrate with Dowex No. 1 anion-exchange resin [5] gave *7-amino-3-β-D-glucopyranosyl-v-triazolo*[d]*pyrimidine* as blades (from water), m. p. 241° (decomp.), $[\alpha]_D^{20}$ −22° (*c* 1 in H_2O) (Found: C, 40·2; H, 4·8; N, 27·9. $C_{10}H_{14}O_5N_6$ requires C, 40·3; H, 4·7; N, 28·2%).

Chloromercuri-derivatives.—The triazolopyrimidine was dissolved in cold water (10 vols.) by addition of N-sodium hydroxide (2 equivs. for the diacetyl derivatives of 7-amino-5-methylthio- and 5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine; 1 equiv. in the other cases). To the filtered solution was added mercuric chloride (1 mol.) in hot ethanol (8 c.c. per g.) followed by water (20 vols.) and Hyflo Supercel (1·5 times the weight of triazolopyrimidine). The product was collected after cooling, washed with water, dried, and powdered. Yields were 80—90%.

Reaction of Chloromercuri-derivatives with O-Acylglycosyl Halides.—In the reaction using tetra-*O*-acetylglucosyl bromide the procedure of Davoll and Lowy [8] was followed; those using tri-*O*-benzoyl-D-ribofuranosyl chloride were carried out as described by Kissman *et al.*,[7] except that the final extraction of the crude condensation product with ether was omitted.

[11] Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

XUM

7-*Amino*-v-*triazolo*[d]*pyrimidine*.—4 : 6-Diamino-2-mercaptopyrimidine (35 g.) was nitrosated [11] and the crude wet product then boiled under reflux with stirring for 1 hr. with water (3 l.), ammonia (*d* 0·88; 120 c.c.), and Raney nickel [11] (from 180 g. of alloy). The mixture was filtered hot, and the filtrate evaporated under reduced pressure to 1·2 l., shaken with charcoal, and again filtered. To the filtrate was added glacial acetic acid (75 c.c.) followed by sodium nitrite (13 g.) in water (100 c.c.), added dropwise with stirring. The triazolopyrimidine (13·5 g., 40%) was collected after 1 hr. as an almost white powder.

7-*Acetamido*-v-*triazolo*[d]*pyrimidine*.—The above compound (2 g.) and acetic anhydride (20 c.c.) were boiled together under reflux for 4 hr. Collected after cooling and washed with ethanol, the *acetamido-compound* (2·06 g., 79%) had m. p. 294° (decomp.) and was sufficiently pure for further use. It formed prisms (from 50% aqueous 2-ethoxyethanol), m. p. 293—294° (decomp.) (Found: C, 40·3; H, 3·7; N, 47·2. $C_6H_6ON_6$ requires C, 40·5; H, 3·4; N, 47·2%).

7-*Acetamido*-x-*chloromercuri*-v-*triazolo*[d]*pyrimidine and Tetra*-O-*acetyl*-D-*glucopyranosyl Bromide*.—The reaction between the chloromercuri-compound (9·05 g.) and the bromide (10 g., 1·1 mol.) gave a syrupy product (8·5 g., 77%), which crystallised from ethanol (150 c.c.) to give a compound (0·5 g.) as needles, m. p. 270° after recrystallisation from ethanol (Found: C, 48·1; H, 5·0; N, 11·3, 11·4%). It did not give a crystalline product on deacetylation with methanolic ammonia. The ethanolic filtrate was evaporated, the residue deacetylated with methanolic ammonia at 0°, and the product crystallised from water (25 c.c.), with charcoal, to give (?) 7-*amino*-1-β-D-*glucopyranosyl*-v-*triazolo*[d]*pyrimidine* (0·85 g., 13%), m. p. 250—251° (decomp.), $[\alpha]_D^{23}$ −16° (*c* 0·2 in H_2O) (Found: C, 40·0; H, 4·9; N, 27·7. $C_{10}H_{14}O_5N_6$ requires C, 40·3; H, 4·7; N, 28·2%). The *picrate* formed solvated needles (from 50% ethanol), m. p. 160° (effervescence) (Found: C, 37·5; H, 4·1; N, 22·3. $C_{10}H_{14}O_5N_6,C_6H_3O_7N_3,C_2H_6O$ requires C, 37·7; H, 4·0; N, 22·0%).

Addition of picric acid to the filtrate from the 1-glucosyl compound gave 7-amino-3-β-D-glucopyranosyl-*v*-triazolo[*d*]pyrimidine picrate (1·53 g., 13%), m. p. 183° (decomp.), raised to 202° (decomp.) by several recrystallisations from water (Found: C, 36·3; H, 3·4; N, 24·0%). Removal of picric acid gave the 3-glucosyl derivative, m. p. 241° (decomp.), $[\alpha]_D^{20}$ −24° (*c* 0·93 in H_2O) (Found: C, 40·1; H, 4·8; N, 27·8%). This compound and its picrate did not depress the m. p.s of samples prepared as described above, and the ultraviolet absorption spectrum of the free compound was virtually identical with that of the previous sample.

7-*Amino*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* (" 8-*Aza-adenosine* ").—Condensation of 7-acetamido-*x*-chloromercuri-*v*-triazolo[*d*]pyrimidine (16·7 g.) with tri-*O*-benzoyl-D-ribofuranosyl chloride (1·09 mol.; from 22·1 g. of the 1-acetate) gave a syrupy product (24·5 g., 97%). This was deacylated with sodium methoxide (ref. 7, note 26), and after neutralisation with carbon dioxide the mixture was evaporated and the residue triturated with dry ether to remove methyl benzoate, and dried. Crystallisation from water (125 c.c.) with charcoal, followed by evaporation to 30 c.c. to obtain a second crop, gave a total of 1·69 g. (16%) of the 3-β-D-*ribofuranosyl compound* as needles, m. p. 209—218°, raised to 218—219° by recrystallisation from water, $[\alpha]_D^{23}$ −79° (*c* 0·46 in H_2O) (Found: C, 40·5; H, 4·9; N, 31·4. $C_9H_{13}O_4N_5$ requires C, 40·3; H, 4·5; N, 31·3%). The *picrate* separated from water in needles, m. p. 184° (decomp., previous darkening) (Found: C, 36·1; H, 3·2; N, 25·6. $C_9H_{13}O_4N_5,C_6H_3O_7N_3$ requires C, 36·2; H, 3·0; N, 25·4%).

Addition of picric acid to the mother-liquor from the above riboside gave a picrate (7·25 g.) which could not be purified; removal of picric acid gave a product which formed gelatinous solutions in water and did not crystallise. Its ultraviolet absorption spectrum showed maxima at 273 mμ (in 0·1N-hydrochloric acid) and 287 mμ (in 0·1N-NaOH).

7-*Hydroxy*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* (" 8-*Azainosine* ").—A solution of 7-amino-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (2 g.) and sodium nitrite (5 g.) in hot water (25 c.c.) was cooled rapidly and treated with glacial acetic acid (5 c.c.). After 1 hr. water (25 c.c.) was added, and after 18 hr. the product (1·87 g.) was isolated by precipitation with excess of aqueous lead acetate and ammonia, treatment of the lead salt in 20% acetic acid with hydrogen sulphide, and evaporation of the lead sulphide filtrate. The 7-*hydroxy-compound* (1·38 g., 69%) separated from 80% ethanol (60 c.c.) as prisms or needles, m. p. 196—197°, raised to 199—200° by recrystallisation, $[\alpha]_D^{21}$ −54° (*c* 1·78 in H_2O) (Found: C, 40·2; H, 4·4; N, 26·3. $C_9H_{11}O_5N_5$ C, 40·2; H, 4·1; N, 26·0%).

[11] Bendich, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1948, **70**, 3109.

XUM

5 : 7-*Diamino*-v-*triazolo*[d]*pyrimidine*.—To a solution of 2 : 4 : 6-triaminopyrimidine [13] (8·5 g.) in 10% acetic acid (220 c.c.) was added sodium nitrite (4·85 g.) in water (30 c.c.), dropwise, with stirring. After 1 hr. glacial acetic acid (115 c.c.) and 5% palladised charcoal were added, and the mixture was shaken in hydrogen, 2 mols. being absorbed in 1 hr. After removal of catalyst the almost colourless filtrate was treated with sodium nitrite (4·85 g.) in water (30 c.c.) added dropwise with stirring. The separated product was treated with charcoal in hot dilute aqueous ammonia, and the hot filtrate acidified with acetic acid, giving the *diamino-compound* (7·55 g., 73%) as a white powder (Found: N, 64·3. $C_4H_5N_7$ requires N, 64·9%).

5 : 7-*Diacetamido*-v-*triazolo*[d]*pyrimidine*.—The above diamino-compound (9·76 g.) and acetic anhydride (98 c.c.) were boiled together under reflux for 30 min. The *triacetyl compound* (13·3 g., 75%), m. p. 210° (decomp.) (Found: N, 35·4. $C_{10}H_{11}O_3N_7$ requires N, 35·4%), was collected after cooling and washed with ethanol. When this was heated to the b. p. with 2-ethoxyethanol (200 c.c.) containing a little water the *diacetamido-derivative* (9·94 g., 61% overall yield), m. p. 280° (decomp.), separated from the hot solution and was collected after cooling and washed with ethanol. It separated from 2-ethoxyethanol as hydrated needles of unchanged m. p. (Found: C, 38·7; H, 4·5; N, 38·6. $C_8H_9O_2N_7,H_2O$ requires C, 37·9; H, 4·4; N, 38·7%).

5 : 7-*Diacetamido*-x-*chloromercuri*-v-*triazolo*[d]*pyrimidine and Tri*-O-*benzoyl*-D-*ribofuranosyl Chloride*.—Condensation between the chloromercuri-compound (8 g.) and tri-*O*-benzoyl-D-ribofuranosyl chloride (1 mol.; from 8·56 g. of the 1-acetate) gave a pale yellow glass (11·4 g., 98%). Deacylation with sodium methoxide [7] and crystallisation of the product from water (15 c.c.) gave the 5 : 7-*diamino*-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine*(s) (2·03 g., 42%), m. p. 127—150°, unchanged by further recrystallisation from water (Found: C, 37·8; H, 5·0; N, 34·5. $C_9H_{13}O_4N_7$ requires C, 38·2; H, 4·6; N, 34·6%).

5 : 7-*Diamino*-3-*methyl*-v-*triazolo*[d]*pyrimidine*.—2 : 4-Diamino-6-chloropyrimidine (3 g.) and benzylmethylamine (9 c.c.) were boiled together under reflux for 1 hr. The cooled mixture was extracted with boiling ethyl acetate (60 c.c.), the extract washed with 5% acetic acid, dried (Na_2SO_4), and evaporated, and the residue crystallised from ethyl acetate, to give 2 : 4-*diamino*-6-(N-*methylbenzylamino*)*pyrimidine acetate* (2·15 g., 36%), m. p. 146—148° (Found: C, 58·0; H, 6·9; N, 24·6. $C_{12}H_{15}N_5,C_2H_4O_2$ requires C, 58·1; H, 6·6; N, 24·2%). This material was nitrosated in the usual way in 20% acetic acid, and the product suspended in 50% acetic acid and hydrogenated in presence of 10% palladised charcoal. Three mols. of hydrogen were absorbed, and addition of 1 mol. of aqueous sodium nitrite to the filtered solution gave 5 : 7-*diamino*-3-*methyl*-v-*triazolo*[d]*pyrimidine* (84%) as laths (from water), m. p. 294—295° (Found: C, 36·1; H, 4·5; N, 59·4. $C_5H_7N_7$ requires, C, 36·4; H, 4·3; N, 59·4%). The compound was insoluble in alkali, excluding the possible structure 5-amino-7-methylamino-*v*-triazolo[*d*]-pyrimidine.

(?) 5-*Amino*-7-*hydroxy*-1-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine*.—(*a*) The crude condensation product (18·9 g.) from 5 : 7-diacetamido-*x*-chloromercuri-*v*-triazolo[*d*]pyrimidine and tri-*O*-benzoyl-D-ribofuranosyl chloride was deacylated with methanolic ammonia, treated with nitrous acid, and finally deacylated with sodium methoxide, according to the general procedure for guanine derivatives,[5] without crystallisation of intermediates. The *5-amino-7-hydroxy-compound* (1·26 g., 16%) crystallised without purification through the lead salt; it formed needles (from water), which decomposed without melting above 200° and had $[\alpha]_D^{20}$ −75° (*c* 0·9 in H_2O) (Found: C, 37·7; H, 4·6; N, 29·4. $C_9H_{13}O_5N_5$ requires C, 38·0; H, 4·3; N, 29·6%). Hydrolysis for 2 hr. with boiling N-hydrochloric acid gave material with the spectrum of 5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine.

(*b*) The crystalline 5 : 7-diamino-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine(s) described above (0·45 g.) was boiled under reflux for 45 min. with acetic anhydride (5 c.c.). Evaporation and treatment as described in (*a*) gave the same 5-amino-7-hydroxy-compound (0·11 g., 24%), identified by its ultraviolet absorption spectrum in acid and alkali.

2-*Methylthio*-9-β-D-*ribofuranosylhypoxanthine*.—2-Methylthio-9-β-D-ribofuranosyladenine [6] (0·5 g.) in 0·4N-sulphuric acid (100 c.c.) was treated with sodium nitrite (1·2 g.). After 18 hr. the solution was neutralised with ammonia and evaporated to 15 c.c., to give the *hypoxanthine derivative* (0·46 g., 92%) as needles (from water), m. p. 246° (decomp., with darkening above 210°) (Found: C, 41·7; H, 4·5; N, 17·4. $C_{11}H_{14}O_5N_4S$ requires C, 42·0; H, 4·5; N, 17·8%).

[13] Sato, Nakajima, and Tanaka, *J. Chem. Soc. Japan, Pure Chem. Sect.*, 1951, **72**, 866 (*Chem. Abs.*, 1953, **47**, 5946e).

XUM

Guanosine.—The above compound (0·5 g.), aqueous ammonia (*d* 0·88; 4 c.c.), and ethanolic ammonia (4 c.c., saturated at 0°) were heated together in a sealed tube for 18 hr. at 130—132°. Evaporation of the cooled mixture and four crystallisations of the residue from water (charcoal) gave guanosine (0·12 g., 24%) as colourless needles which charred above 230° alone or in admixture with the natural nucleoside and had $[\alpha]_D^{24}$ −72° (*c* 0·96 in 0·1N-NaOH) {reported [5] for natural guanosine: $[\alpha]_D^{23}$ −70° (*c* 1·15 in 0·1N-NaOH)} (Found: C, 42·1; H, 4·6; N, 25·1. Calc. for $C_{10}H_{13}O_5N_5$: C, 42·4; H, 4·6; N, 24·7%). The infrared spectra of samples of the natural and synthetic compounds (as dihydrates, in Nujol mull), and their ultraviolet absorption spectra, were indistinguishable.

7-*Amino*-5-*methylthio*-v-*triazolo*[d]*pyrimidine.*—4 : 5 : 6-Triamino-2-methylthiopyrimidine (1·71 g.) in 10% acetic acid (55 c.c.) was treated with sodium nitrite (0·69 g.) in a little water. The precipitate was treated with charcoal in hot dilute aqueous ammonia and acidified with acetic acid, to give the *triazolopyrimidine* (1·55 g., 81%) as a hydrated powder, m. p. 282° (decomp.) (Found: C, 31·7; H, 3·6; N, 44·3. $C_5H_6N_6S,\frac{1}{2}H_2O$ requires C, 31·4; H, 3·7; N, 44·0%).

Acetyl Derivatives of 7-*Amino*-5-*methylthio*-v-*triazolo*[d]*pyrimidine.*—The above material (1 g.) and acetic anhydride (5 c.c.) were boiled together under reflux for 2 hr. Addition of dry ether (10 c.c.) to the cooled mixture gave the slightly impure *diacetyl compound* (1·06 g., 76%) as pale yellow crystals, m. p. 153—155° (Found: C, 41·3; H, 4·5; N, 30·5. $C_9H_{10}O_2N_6S$ requires C, 40·6; H, 3·8; N, 31·6%).

During several months in air one acetyl group was lost with formation of 7-*acetamido*-5-*methylthio*-v-*triazolo*[d]*pyrimidine*, m. p. 215—217° (Found: C, 38·1; H, 4·1. $C_7H_8ON_6S$ requires C, 37·5; H, 4·6%), which separated as solvated needles, m. p. 219—220°, from 70% ethanol (Found: C, 39·0; H, 5·1; N, 31·5. $C_7H_8ON_6S,C_2H_6O$ requires C, 40·0; H, 5·2; N, 31·1%).

7-*Acetamido*-x-*chloromercuri*-5-*methylthio*-v-*triazolo*[d]*pyrimidine and Tri*-O-*benzoyl*-D-*ribofuranosyl Chloride.*—The syrupy condensation product (31 g., 96%) obtained from the chloromercuri-compound (23 g.) and tri-*O*-benzoyl-D-ribofuranosyl chloride (1 mol.; from 25·4 g. of the 1-acetate) was deacylated with sodium methoxide,[7] and the product dissolved in hot water (175 c.c.) and treated with charcoal. A first crop (3·79 g., 24%), m. p. 193—197°, was collected after 1½ hr. at room temperature and a second crop (2·8 g., 18%), m. p. 142—150°, after a further 20 hr. at 3°.

Recrystallisation of the first crop from water gave 7-*amino*-5-*methylthio*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* as needles, m. p. 200—201° (Found: C, 37·7; H, 4·6; N, 26·7. $C_{10}H_{14}O_4N_6S$ requires C, 38·2; H, 4·5; N, 26·7%).

The second crop on recrystallisation from water gave (?) 7-*amino*-5-*methylthio*-1-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* as needles, m. p. 156—158° (Found: C, 38·0; H, 4·8; N, 26·8%).

7-*Amino*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine from its* 5-*Methylthio-derivative.*—The above 5-methylthio-compound of m. p. 200—201° with acetic anhydride–pyridine at room temperature gave 7-*amino*-3-*tri*-O-*acetyl*-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* (84%), as prisms (from ethanol), m. p. 152—153° (Found: C, 43·7; H, 4·8. $C_{16}H_{20}O_7N_6S$ requires C, 43·6; H, 4·6%). The triacetyl derivative (0·14 g.) was boiled for 2 hr. in ethanol (10 c.c.) with Raney nickel [11] (*ca.* 1 g.), and the product deacetylated with methanolic ammonia and crystallised from water, to give 7-amino-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (18 mg., 21%), m. p. and mixed m. p. 216—217° (Found: N, 31·3%). The ultraviolet absorption spectrum in acid and alkali was virtually identical with that of authentic material.

Desulphurisation of (?)7-*Amino*-5-*methylthio*-1-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine.*—The above procedure yielded an amorphous product, which gave gelatinous solutions in water and showed ultraviolet absorption maxima at 285 mμ (in 0·1N-HCl) and 292 mμ (in 0·1N-NaOH).

7-*Hydroxy*-5-*methylthio*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine.*—A solution of 7-amino-5-methylthio-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (0·5 g.) in N-nitric acid (100 c.c.) was treated with sodium nitrite (1·2 g.). After 20 hr. at room temperature the 7-*hydroxy-compound* (0·43 g., 86%) was collected; it formed leaflets (from water), m. p. 181—183° (with sintering above 178°) (Found: C, 37·5; H, 4·1; N, 22·7. $C_{10}H_{13}O_5N_5S$ requires C, 38·1; H, 4·2; N, 22·2%).

5-*Amino*-7-*hydroxy*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* ("8-*Azaguanosine*").—The above methylthio-compound (0·5 g.) was aminated as described under the preparation of

guanosine. Isolated through the lead salt and crystallised from water (1 c.c.), the 5-amino-7-hydroxy-compound (40 mg., 8%) formed needles, m. p. 250—252° (decomp.) (Found: N, 29·8. Calc. for $C_9H_{13}O_5N_6$: N, 29·6%). After hydrolysis of the compound with boiling N-hydrochloric acid for 2 hr. the ultraviolet spectrum was essentially that of 5-amino-7-hydroxy-*v*-triazolo-[*d*]pyrimidine (max. at 250 mμ in 0·1N-HCl), but the shoulder at 266mμ was obscured. When more concentrated acid was used for the hydrolysis the absorption shifted to longer wavelengths; with 6N-hydrochloric acid for 30 min.[9] the absorption in 0·1N-hydrochloric acid showed a maximum at 270 mμ, with a shoulder at 255 mμ. A similar curve was obtained when 5-amino-7-hydroxy-*v*-triazolo[*d*]pyrimidine and ribose were heated together under the same acid conditions, but not when either component was omitted.

(?)7-*Hydroxy*-5-*methylthio*-1-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine*.—A solution of the 7-amino-compound (0·5 g.) and sodium nitrite (1·2 g.) in hot water (12 c.c.) was cooled rapidly and treated with glacial acetic acid (1·2 c.c.). After 24 hr. the 7-*hydroxy-compound* (0·28 g., 56%) was isolated through the lead salt; it formed needles (from water), m. p. 214—215° (Found: C, 38·0; H, 4·2; N, 21·9. $C_{10}H_{13}O_5N_5S$ requires C, 38·1; H, 4·2; N, 22·2%).

Diacetyl Derivative of 5-*Amino*-7-*hydroxy*-v-*triazolo*[d]*pyrimidine*.—The triazolopyrimidine (15·5 g.) and acetic anhydride (155 c.c.) were boiled together under reflux for 2 hr. Collected after cooling and washed with ethanol, the *diacetyl derivative* (23·2 g.; 96%) formed needles, m. p. 219° (decomp.) (Found: C, 40·6; H, 4·2; N, 35·4. $C_8H_9O_5N_5$ requires C, 40·7; H, 3·4; N, 35·6%).

5-*Acetamido*-x-*chloromercuri*-7-*hydroxy*-v-*triazolo*[d]*pyrimidine and Tri*-O-*benzoyl*-D-*ribofuranosyl Chloride*.—Condensation of the chloromercuri-compound (31 g.) with tri-*O*-benzoyl-D-ribofuranosyl chloride (1·15 mol.; from 42 g. of the 1-acetate) gave a pale yellow gum (41·5 g., 90%), which was boiled under reflux for 1 hr. with a solution of sodium methoxide prepared from sodium (2·5 g.) and methanol (400 c.c.). The mixture was evaporated to dryness and a solution of the residue in water (500 c.c.) was made just acidic with acetic acid, heated to boiling, and treated with charcoal. A first crop (7·33 g.) was collected after 18 hr. at room temperature; the filtrate was then evaporated to 200 c.c., then cleared by heat, and a second crop (4·62 g.) collected after 5 hr. A third crop (4·13 g.) was obtained by evaporating the mother-liquors to 50 c.c.

The first crop on recrystallisation gave (?)5-*amino*-7-*hydroxy*-2-β-D-*ribofuranosyl*-v-*triazolo*-[d]*pyrimidine* (6·28 g.) as needles (from water), sintering at 230—235°, $[\alpha]_D^{20}$ −79° (*c* 0·77 in 0·1N-NaOH) (Found: C, 37·8; H, 4·8; N, 29·1. $C_9H_{12}O_5N_6$ requires C, 38·0; H, 4·3; N, 29·6%).

Recrystallisation of the second crop gave 5-amino-7-hydroxy-3-β-D-ribofuranosyl-*v*-triazolo-[*d*]pyrimidine (3·9 g.), m. p. 251—253° (decomp.), undepressed by admixture with the material obtained by the other route, $[\alpha]_D^{21}$ −97° (*c* 1·0 in 0·1N-NaOH) (Found: C, 38·3; H, 4·3; N, 28·9. Calc. for $C_9H_{12}O_5N_6$: C, 38·0; H, 4·3; N, 29·6%).

The third crop contained about 85% of the 3-ribofuranosyl derivative, but further purification of this material by recrystallisation was difficult. On deamination (see below), however, it yielded pure 5 : 7-dihydroxy-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (m. p. and mixed m. p.).

5 : 7-*Dihydroxy*-3-β-D-*ribofuranosyl*-v-*triazolo*[d]*pyrimidine* (" 8-*Azaxanthosine* ").—A solution of 5-amino-7-hydroxy-3-β-D-ribofuranosyl-*v*-triazolo[*d*]pyrimidine (0·3 g.) and barium nitrite monohydrate (1 g.) in hot water (4 c.c.) was cooled rapidly and treated with glacial acetic acid (1 c.c.). After 5 hr. barium was removed by addition of one equivalent (8·06 c.c.) of N-sulphuric acid. Evaporation of the filtrate below 15° and crystallisation of the residue from 5 : 2 ethanol–water (4 c.c.) gave the *dihydroxy-compound* (0·14 g., 47%) as needles, m. p. 198—199° (decomp.) after recrystallisation, $[\alpha]_D^{24}$ −103° (*c* 1·02 in 0·1N-NaOH) (Found: C, 37·4; H, 3·9; N, 24·5. $C_9H_{11}O_6N_5$ requires C, 37·9; H, 3·9; N, 24·6%).

The author thanks Dr. R. E. Bowman for many helpful discussions, and Miss E. M. Tanner for determination of the spectra.

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XUM

319. *Tocopherols. Part I. Synthesis of 7-Methyltocol (η-Tocopherol).*

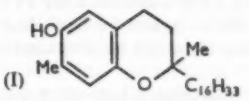
By D. McHale, P. Mamalis, J. Green, and S. Marcinkiewicz.

Racemic 7-methyltocol has been synthesised by an unambiguous route and found to have paper-chromatographic properties identical with those of natural η-tocopherol.

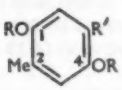
A comparison of the ultraviolet absorption spectra of tocol and all the *Bz*-methyltocols is included.

Recently Green and Marcinkiewicz [1] reported the isolation of 7-methyltocol (η-tocopherol) (I) from the lipid fraction of rice and thus showed that all the seven possible *Bz*-methylated tocols occurred in Nature. It was possible that the 7-methyltocol obtained from rice contained a small amount of 5-methyltocol (ε-tocopherol) which would be virtually undetectable in the presence of the 7-methyltocol, and thus it was apparent that a synthesis of 7-methyltocol free from other tocopherols would be of value to provide a sample for analytical and biological studies.

Karrer and Fritzsche [2] prepared 7-methyltocol in admixture with other monomethyltocols by direct condensation of toluquinol and phytol. Work in this laboratory [3] has shown that 5-, 7-, and 8-methyltocol are formed in this reaction. An attempt by Karrer and Dutta [4] to prepare 5- and 7-methyltocol by the condensation of methylthiotoluquinols with phytol and subsequent desulphurisation with Raney Nickel was inconclusive because the starting material condensed and cyclised in two directions. Using the paper-chromato-



(I)



(II)

graphic technique of Green, Marcinkiewicz, and Watt [5] to identify the products, repetition of this work indicated that Karrer and Dutta incorrectly assumed the configuration of one of the methylthiotoluquinols: their 8-methyltocol was in fact 7-methyltocol, which almost certainly contained some 5-methyltocol (this work will be reported in full in a paper relating to the synthesis of 5-methyltocol).

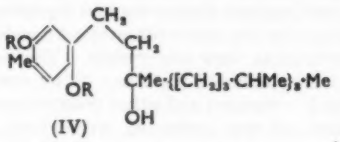
Because of the difficulty in separating mixtures of methyltocols, an unambiguous preparation was required and for this purpose the method used by Smith and Miller [6] for α-tocopherol was adapted. The chroman was built by known reactions leading *via* intermediates of unambiguous structure to the final product (I).

Toluquinol (II; R = R′ = H) was brominated to yield the known 5-bromotoluquinol [7] (II; R = H, R′ = Br). The conversion of this compound into 5-bromotoluquinol dimethyl ether (II; R = Me, R′ = Br) by the method of Smith, Wawzonek, and Miller [8] proceeded only in low yield, but the use of methyl iodide and potassium carbonate in acetone gave an almost quantitative yield. The bromo-ether was converted, by an entrainment technique with ethyl iodide, into a Grignard reagent (II; R = Me, R′ = MgBr) which gave with ethylene oxide 5-2′-hydroxyethyltoluquinol dimethyl ether (II; R = Me, R′ = CH_2·CH_2·OH). Treatment with phosphorus tribromide then yielded 5-2′-bromoethyltoluquinol dimethyl ether (II; R = Me, R′ = CH_2·CH_2Br) from which the Grignard

[1] Green and Marcinkiewicz, *Nature*, 1956, **176**, 86.
[2] Karrer and Fritzsche, *Helv. Chim. Acta*, 1939, **22**, 260.
[3] Mamalis, McHale, Green, and Marcinkiewicz, unpublished work.
[4] Karrer and Dutta, *Helv. Chim. Acta*, 1948, **31**, 2080.
[5] Green, Marcinkiewicz, and Watt, *J. Sci. Food Agric.*, 1955, **6**, 274.
[6] Smith and Miller, *J. Amer. Chem. Soc.*, 1942, **64**, 440.
[7] Clark, *Amer. Chem. J.*, 1892, **14**, 569.
[8] Smith, Wawzonek, and Miller, *J. Org. Chem.*, 1941, **6**, 229.

derivative was prepared by the entrainment technique with ethyl iodide. This Grignard derivative on reaction with the ketone (III) yielded a mixture of 5-(3-hydroxy-3 : 7 : 11 : 15-tetramethylhexadecyl)toluquinol dimethyl ether (IV; R = Me) and probably 3 : 7 : 11 : 15-tetramethylhexadecan-3-ol (V), the latter resulting from the reaction of ethylmagnesium iodide and ketone (III). Demethylation and cyclisation were carried out on the mixture, vacuum-distillation of the product yielding an oil containing approximately 30% of 7-methyltocol. A 70% concentrate was obtained after adsorption on a zinc carbonate column and was suitable for the preparation of the derivatives, *e.g.*, the 3 : 5-dinitrophenylurethane and the 4-phenylazobenzoate were prepared. The latter derivative, on hydrolysis and molecular distillation, yielded pure 7-methyltocol, whose paper chromatographic behaviour was identical with that of natural γ_1-tocopherol.

The ketone (III) was derived from phytol by ozonolysis in methylene chloride containing a small amount of pyridine. This solvent mixture gave a higher yield of a purer product than that obtained by using Smith and Miller's conditions.[6]



(IV)

Me·{CHMe·[CH$_2$]$_3$}$_3$·COMe (III)

Me·{CHMe·[CH$_2$]$_3$}$_3$·CMeEt·OH (V)

It had originally been the intention to use the dibenzyl ether throughout the synthesis, but although 5-bromotoluquinol dibenzyl ether (II; R = Ph·CH$_2$, R′ = Br) was readily obtained, it was not possible to form a Grignard derivative from this compound. This was in agreement with the fact that Smith and Miller [6] could not form a Grignard derivative from bromotrimethylquinol dibenzyl ether.

Eggitt and Norris [9] previously compared the ultraviolet absorption spectra of five of the tocopherols. 7-Methyltocol, 5 : 7-dimethyltocol, and tocol [10] itself were not included and for this reason a completed list is given in the annexed Table. The 5 : 7-dimethyltocol

Comparison of the ultraviolet absorption spectra of the tocopherols.

Tocopherol	Wavelength at minimum (mμ)	Wavelength at maximum (mμ)	$E^{1\%}_{1\,cm.}$ at max.
Tocol	255	298·5	97
5-Methyltocol	257·5	295·5	87·5
7-Methyltocol	255	298	103
8-Methyltocol	257	298	87·3
5 : 7-Dimethyltocol	255	292	83·0
5 : 8-Dimethyltocol	257·5	296	89·4
7 : 8-Dimethyltocol	257	298	91·4
5 : 7 : 8-Trimethyltocol	256	292	75·8

was synthesised by the original method of Karrer and Fritzsche [11] but purification was through the 4-phenylazobenzoate and not by chromatography. Pure 5 : 7-dimethyltocol, which crystallised in prisms at −4°, is the first racemic tocopherol to be obtained crystalline.

Experimental

5-Bromotoluquinol (II; R = H, R′ = Br).—To a stirred and cooled solution of toluquinol (49·6 g.) in dry ether (100 ml.) was added, dropwise, bromine (64 g.) in dry chloroform (50 ml.).

[9] Eggitt and Norris, *J. Sci. Food Agric.*, 1955, **6**, 689.
[10] Mamalis, McHale, Green, and Marcinkiewicz, unpublished work.
[11] Karrer and Fritzsche, *Helv. Chim. Acta*, 1938, **21**, 1234.

5-Bromotoluquinol separated almost immediately and crystallisation was completed by addition of chloroform (400 ml.). Recrystallisation from water, containing sufficient ethanol to bring about solution, gave the bromo-compound (55 g.), m. p. 182—184° (Found: C, 41·6; H, 3·5; Br, 39·2. Calc. for $C_7H_7O_2Br$: C, 41·4; H, 3·5; Br, 39·3%) (Clark [7] gave m. p. 179°).

5-Bromotoluquinol Dimethyl Ether (II; R = Me, R′ = Br).—Methyl iodide (37 g.) was added rapidly to a stirred mixture of 4-bromotoluquinol (25 g.), anhydrous potassium carbonate (34 g.), and acetone (150 ml.) and the whole refluxed for 3 hr. The product was isolated by steam-distillation, and recrystallisation from aqueous ethanol gave the *ether* (26 g.) as prisms, m. p. 91° (Found: C, 46·8; H, 4·8; Br, 34·5. $C_9H_{11}O_2Br$ requires C, 46·8; H, 4·8; Br, 34·6%).

5-Bromotoluquinol Dibenzyl Ether (II; R = Ph·CH_2, R′ = Br).—This was obtained from 5-bromotoluquinol (3·2 g.) by the method Smith and Miller [6] used for bromotrimethylquinol dibenzyl ether. Crystallised from light petroleum (b. p. 80—100°) the *ether* (3·8 g.) had m. p. 131° (Found: C, 65·5; H, 4·8; Br, 20·9. $C_{21}H_{19}O_2Br$ requires C, 65·8; H, 5·0; Br, 21·1%).

5-2′-Hydroxyethyltoluquinol Dimethyl Ether (II; R = Me, R′ = CH_2·CH_2·OH).—4-Bromotoluquinol dimethyl ether (23·1 g.) and ethyl iodide (15·6 g.) in dry ether (100 ml.) were added slowly, with stirring, to magnesium turnings (4·8 g.) activated with a crystal of iodine and gently heated on a steam-bath. After 2 hours' refluxing, the Grignard derivative had separated; the suspension was cooled to 0°, and ethylene oxide (15 g.) in dry ether (35 ml.) was added with stirring (inefficient stirring of the thick suspension leads to very low yields). The resulting mixture was allowed to come to room temperature, then refluxed for 2 hr. After cooling, it was hydrolysed by ice-cold 25% sulphuric acid (50 ml.). Butanol and other volatile impurities were removed by steam-distillation and the residual oil was extracted with ether. After removal of solvent, distillation gave the *hydroxyethyl compound* (13·5 g.), b. p. 123—124°/0·2 mm., m. p. 58—59° [from light petroleum (b. p. 40—60°)] (Found: C, 67·8; H, 7·7. $C_{11}H_{14}O_3$ requires C, 67·3; H, 8·2%).

5-2′-Bromoethyltoluquinol Dimethyl Ether (II; R = Me, R′ = CH_2·CH_2Br).—Phosphorus tribromide (23 g.) in light petroleum (100 ml.; b. p. 80—100°) was added slowly to a stirred solution of the hydroxyethyl compound (20 g.) in light petroleum (250 ml.; b. p. 80—100°) at 50°. After 2 hr., the mixture was cooled and hydrolysed by water (100 ml.), and the organic layer was washed successively with water, saturated aqueous sodium hydrogen carbonate, and water, dried, and evaporated. Crystallization from aqueous methanol gave the *bromoethyl compound* (12·1 g.), m. p. 56—58° (Found: C, 51·0; H, 5·8; Br, 30·8. $C_{11}H_{15}O_2Br$ requires C, 51·0; H, 5·8; Br, 30·8%).

When kept, the original aqueous layer deposited needles which contained no bromine and on recrystallization from ethyl acetate had m. p. 93—94°. This compound was assumed to be the *dihydrogen phosphite* of the hydroxyethyl compound [II; R = Me, R′ = CH_2·CH_2·O·P(OH)$_2$] (Found: C, 51·2; H, 6·4. $C_{11}H_{17}O_5P$ requires C, 50·9; H, 6·6%).

6 : 10 : 14-Trimethylpentadecan-2-one (III).—Phytol (12 g.) in methylene chloride (200 ml.) containing pyridine (12 ml.) was ozonised [ozone (0·6 g.) in oxygen (20 l./hr.)] at 0° until absorption was complete. After reductive cleavage by zinc dust (10·9 g.) in acetic acid (13 ml.), the hydroxylic impurities were removed by washing, and distillation yielded the ketone (7·3 g.), b. p. 120—130°/0·2 mm., n_D^{24} 1·4441 (Lukes and Zobacova [13] gave b. p. 132—134°/1 mm., n_D^{25} 1·4434).

7-Methyltocol (I).—The bromoethyl compound (2·6 g.) and ethyl iodide (1·6 g.) in dry ether were added slowly to magnesium turnings (0·48 g.) activated by a crystal of iodine, and the whole was refluxed for 4—5 hr., then cooled to 0°. The ketone (III) (5·4 g.) was added dropwise and the mixture refluxed for a further 2 hr., cooled, and hydrolysed by dilute hydrochloric acid. The ether layer yielded on evaporation a mixture (7·8 g.) of alcohols (IV) and (V) which was refluxed for 8 hr. with hydrobromic acid (10 g.) in acetic acid (100 ml.). The product was diluted with light petroleum (100 ml., b. p. 40—60°) and washed successively with water, saturated aqueous sodium hydrogen carbonate, dilute hydrochloric acid, and water. Evaporation yielded a pale brown oil (6·6 g.) which contained 14% of the tocol. Distillation yielded two fractions: (*a*) a pale yellow mobile oil (2·9 g.), b. p. 140°/0·1 mm.; (*b*) a yellow viscous oil (2·0 g.), b. p. 220°/0·1 mm. The high-boiling fraction contained 42% of the tocol. Further purification was carried out by adsorption from light petroleum (b. p. 40—60°), on several columns (30 × 2·5 cm.) of zinc carbonate–Hyflo Supercel (1 : 1), previously treated with sodium fluorescein in methanol and activated at 150° for 1 hr. After development with light

[13] Lukes and Zobacova, *Chem. Listy*, 1957, **51**, 330.

petroleum–benzene the band due to the tocol was detected by its quenching of the fluorescence under ultraviolet light. The column was cut and the tocol extracted with ether. Evaporation yielded a pale brown, viscous oil (1·2 g.), which assayed as 70% 7-methyltocol.

This concentrate (0·2 g.) in dry ethylene chloride (5 ml.), containing pyridine (0·4 ml.), was treated with 4-phenylazobenzoyl chloride (0·2 g.) in dry ethylene chloride (5 ml.) and refluxed for 1 hr. Water (2 ml.) was added and after 1 hr. the product was taken up in light petroleum (b. p. 40—60°) and washed with dilute hydrochloric acid and then with water. The organic layer was filtered from the insoluble 4-phenylazobenzoic acid and evaporated. The oil was redissolved in light petroleum, and the solution filtered; on evaporation it yielded a red oil (0·2 g.) which eventually solidified and, after recrystallisation from propan-2-ol, had m. p. 55—56°. It appeared that the *4-phenylazobenzoate* crystallised with solvent of crystallisation which was rapidly lost on filtration, the solid changing from needles into a waxy solid (Found: C, 78·1; H, 8·8; N, 4·3. $C_{46}H_{54}O_3N_2$ requires C, 78·7; H, 8·8; N, 4·6%).

The azobenzoate (0·1 g.) was refluxed in ethanol–propan-2-ol (10 ml.; 1 : 1) and two pellets of potassium hydroxide were added down the condenser. After 20 minutes' refluxing, concentrated hydrochloric acid (2 ml.) was added to the refluxing solution. The inorganic salt was dissolved in water and the organic layer was taken up in light petroleum (b. p. 40—60°). The aqueous layer was separated, and the organic layer was washed several times with water, filtered from 4-phenylazobenzoic acid, and evaporated to a yellow oil (69 mg.). Short-path distillation [150° (bath)/10^{-4} mm.] gave *7-methyltocol* (54 mg.) as a pale yellow oil (Found: C, 81·0; H, 11·8. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%), $\lambda_{max.}$ 298 mμ ($E^{1\%}_{1cm.}$ 104·1), $\lambda_{min.}$ 255 mμ in EtOH, $\nu_{max.}$ 3370 m, 2890 vs, 1620 w, 1500 s, 1455 vs, 1410 s, 1370 s, 1340 m, 1240 m, 1175 vs, 1100 m, 1005 m, 935 m, 909 m, 885 m, 870 s, 813 w cm.$^{-1}$ (liquid film). On assay by the method of Green *et al.*,[5] a spectrophotometric factor of 88·3 was obtained and the development of colour was complete after 2 min.

7-Methyltocol 3′ : 5′-Dinitrophenylurethane.—7-Methyltocol 70% concentrate (0·3 g.) and 3 : 5-dinitrobenzazide (0·4 g.) in dry toluene (5 ml.) were refluxed for 1 hr., during which nitrogen was evolved. The yellow solution was diluted with light petroleum (b. p. 40—60°), filtered from 3 : 5-dinitrophenylurea, and evaporated. The resulting oil solidified on treatment with ethanol–water and gave the *3′ : 5′-dinitrophenylurethane* (0·15 g.), m. p. 115—117° (from ethanol–water) (Found: C, 67·2; H, 8·1; N, 7·0. $C_{34}H_{49}O_7N_3$ requires C, 66·8; H, 8·1; N, 6·9%).

5 : 7-Dimethyltocol.—2 : 6-Dimethylquinol (5 g.), treated with phytol by the method of Karrer and Fritzsche,[11] yielded a yellow oil (13 g.), which contained 61% of the tocol. Vacuum-distillation gave a main fraction, b. p. 200—220°/0·05 mm., containing 87·5% of the tocol. The *4-phenylazobenzoate*, prepared as above, had m. p. 61° (from propan-2-ol) (Found: C, 79·2; H, 8·8; N, 4·2. $C_{41}H_{56}O_3N_2$ requires C, 78·8; H, 9·0; N, 4·5%). Hydrolysis and short-path distillation, as above, yielded *5 : 7-dimethyltocol* as a pale yellow oil which tended to crystallise in prisms at −4°; $\lambda_{max.}$ 292 mμ ($E^{1\%}_{1cm.}$ 83·0), $\lambda_{min.}$ 255 mμ in EtOH; $\nu_{max.}$ 3450 m, 2920 vs, 1460 s, 1375 m, 1340 m, 1320 m, 1245 m, 1220 m, 1155 m, 1105 m, 1050 m, 1020 w, 971 w, 909 w, 885 w, 855 m cm.$^{-1}$ (liquid film). The spectrophotometric factor, determined as for 7-methyltocol, was 93·5.

5 : 7-Dimethyltocol 3′ : 5′-dinitrophenylurethane was prepared as was the 7-methyltocol derivative and crystallised in plates, m. p. 65°, from propan-2-ol–water (Found: C, 67·1; H, 8·2; N, 7·1. $C_{35}H_{51}O_7N_3$ requires C, 67·3; H, 8·2; N, 6·7%).

The authors are grateful to Mr. P. R. Watt for the infrared spectra and to Messrs. P. Ashurst and M. Rix for technical assistance.

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TADWORTH, SURREY.

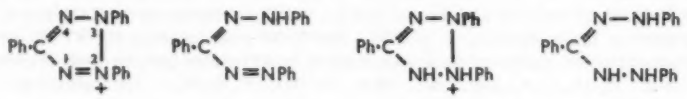
[*Received, December 4th*, 1957.]

320. *Problems Involved in the Polarography of Triphenyltetrazolium Chloride.*

By B. JÁMBOR.

Triphenylformazan gives an oxidation wave which is not due to impurities in the solution. Both the micro- and the macro-cathode reductions of triphenyltetrazolium chloride lead to formazan formation to an extent depending on applied potential, pH, and concentration. The more acid the solution the slower is formazan formation because the reduction will involve $N_{(1)}$ and $N_{(2)}$ instead of $N_{(2)}$ and $N_{(3)}$. Further evidence of this is that a colourless compound is produced, instead of formazan, when triphenyltetrazolium chloride disproportionates under the influence of light in acid medium. Its polarographic wave lies between those of the tetrazolium salt and its photo-derivative. When reduced cathodically, in acid medium, the first step of reduction does not lead to this colourless product, only to its precursor intermediate, of as yet unknown structure, which is reduced further at once. In alkaline medium the first step of reduction proceeds in an analogous way: the first two-electron wave does not indicate formazan formation, but that of its precursor intermediate, from which formazan is formed only secondarily. Since the half-wave potentials, and the character of the half-wave potential–pH curves, of polarograms are much altered by the presence of alcohol, it is only with careful reservations that proton uptake can be deduced from alcoholic solutions.

CAMPBELL and KANE [1] have disagreed with our conclusions from earlier work [2] on the polarography of triphenyltetrazolium chloride (as I). They say that (*a*) as the triphenylformazan (II) produced has no oxidation wave, the system triphenyltetrazolium chloride–triphenylformazan cannot be reversible, and hence that Jámbor's oxidation wave must have been due to impurities in the buffer, and (*b*) neither their results nor ours confirm



(I) (II) (III) (IV)

our view that in acid medium the reduction takes place on the nitrogen atoms 1 and 2 (III). Although these disagreements arise from a difference in methods and a deficiency of experimental results in our earlier paper, we now present further results in support of our views and compare them with those of Campbell and Kane. We further disagree with them that the mechanism of reduction can be derived from the tangent of the half-wave potential–pH curves of 50% methanol–water solutions; this would lead to results improbable from the viewpoint of organic chemistry.

EXPERIMENTAL

Polarograms were prepared as previously.[2] For electrolysis with a stationary mercury cathode an unusually large (100 ml.) Heyrovský vessel was used, in which the mercury pool at the bottom was the cathode and a platinum spiral anode replaced the capillary electrode (Fig. 1).

At a dropping mercury cathode, formazan formation could be seen distinctly around the

[1] Campbell and Kane, *J.*, 1956, 3130.
[2] Jámbor, *Acta Chim. Acad. Sci. Hung.*, 1954, **4**, 55.

drop with a magnifying lens (replacing the horizontal microscope [3]) and a strong light suitably directed. A Methrohm " titriscope " was used in attempts to titrate formazan with alkali.

To prove the reduction involving nitrogen atoms 1 and 2, 10^{-4}M-triphenyltetrazolium chloride at pH 1 under nitrogen was exposed to daylight. Successive samples were polarographed after adjustment to pH 4 (see Fig. 4), and polarograms were also prepared at various pH values from the solution exposed to daylight for 2 hr. to establish the pH-dependence of half-wave potential in the reduction product.

Results and Discussion

(*a*) To decide whether the oxidation wave attributed [2] to formazan was due to impurities, polarograms were prepared of the formazan in ethanol and methanol, and also of the supporting electrolyte. Fig. 2 shows that the oxidation wave is visible for both media containing formazan, but is absent from polarograms of the supporting electrolyte.

Fig. 1. *Cell for macro-electrolysis.*

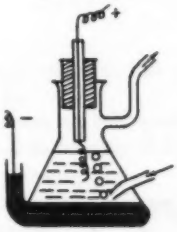
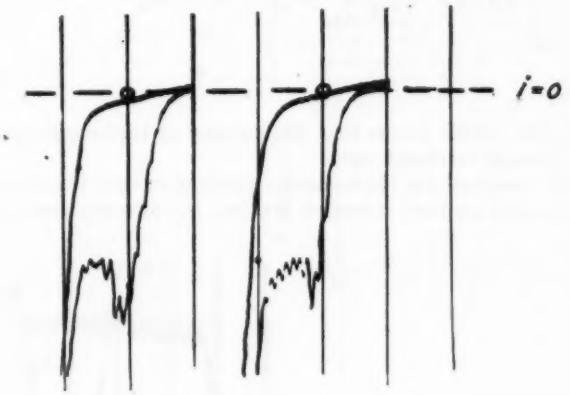


Fig. 2. *Polarograms of triphenylformazan (lower curves) in ethanol (left-hand side) and methanol (right-hand side). The upper curves are of the supporting electrolyte alone. Each horizontal division is* 0·2 v. *Sensitivity* 1/15.



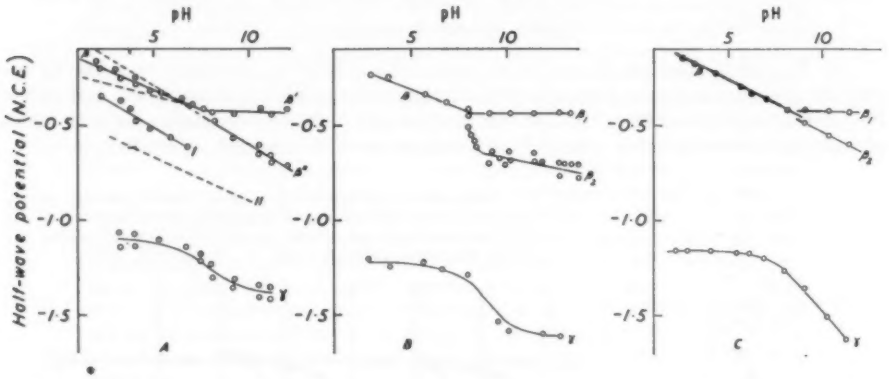
Since the lower horizontal parts of these oxidation waves are obscured by a maximum, particularly in non-automatic polarograms, Campbell and Kane [1] may easily have overlooked the wave. But their Fig. 3 shows that the downward-pointing parts of the polarograms of the tetrazolium chloride and the formazan do not coincide, the curve for the chloride beginning to bend downward at a more positive potential than that of the formazan, so showing that the formazan did produce the wave in question. We agree that, under the conditions of the polarograms in their Fig. 3, the formazan does not produce a wave at the same potential as the tetrazolium chloride does, so that the chloride–formazan system is not *fully* reversible. The formazan produces an anodic wave at a more positive potential. We studied the question of reversibility in alcohol containing concentrated potassium hydroxide, whereas Campbell and Kane used alcohol containing lithium hydroxide, a solution much less alkaline, and we have shown [3,4] that the reversibility of the system increases with pH—at 20° it is complete only above pH 14 and at 70° at pH *ca.* 13. We were also able, by potentiometry of the chloride and the formazan in various proportions, to obtain the sigmoid curve described by the Nernst formula.

In Cambell and Kane's Fig. 3 the β_1 wave of the triphenyltetrazolium salt is separated

[3] Jámbor, *Nature*, 1955, **176**, 603.
[4] Jámbor, *Acta Chim. Acad. Sci. Hung.*, 1957, **13**, 293.

from that of the formazan by *ca.* 0·2 v. We encountered [3] this potential difference in solution of about pH 12·5, whereas our earlier, contested polarograms [2] were prepared at much higher pH's where the distance between the reduction and the oxidation waves was

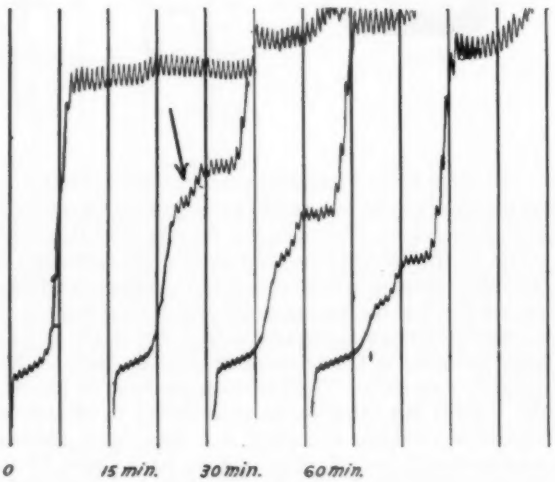
FIG. 3. *Plots of half-wave potential (relative to the normal calomel electrode) against* pH *for the β and γ waves of triphenyltetrazolium chloride, of triphenyltetrazolium chloride reduced at* $N_{(1)}$ *and* $N_{(2)}$ *(I), and of "photo-tetrazolium chloride" (II), obtained (A) in aqueous solution, (B) in 50% ethanol, and (C) the values of Campbell and Kane, obtained in 50% methanol.*



negligible, which means that the mixture of triphenylterazolium salt and the formazan gave a single confluent wave.

(*b*) Campbell and Kane do not regard our or their results as evidence for our assumption that in acid medium reduction involves the nitrogen atoms 1 and 2, instead of 2 and 3,

FIG. 4. *Polarograms of oxygen-free solutions of triphenyltetrazolium chloride exposed to light for various periods. The arrow shows the first production of the colourless compound. Each horizontal division is* 0·2 v. *Sensitivity* 1/5.



but think that the tetrazolium salt is transformed into the benzhydrazyl (IV) by simultaneous uptake of 4 electrons; only at pH > 8 does reduction proceed in two waves *via* formazan. We admit that little evidence was given for the temporary formation of the compound (III) reduced at $N_{(1)}$ and $N_{(2)}$, but neither is the simultaneous uptake of 4 electrons proved.

The essence of our argument is as follows. Formazan has definitely been detected in reductions at pH's less than 7. Furthermore, the formazan concentration increases with pH, which means that the importance of the " formazan reduction route " is a function of pH. Now, because the importance of the formazan reduction route can vary, it follows that there must be some alternative reduction route, which involves an intermediate other than formazan. Experiments with triphenyltetrazolium chloride, which has been exposed to light, suggest that this other intermediate is triphenyltetrazolium chloride, in which reduction has occurred at $N_{(1)}$ and $N_{(2)}$. We had assumed the formation of this colourless compound because the unequal slopes of the half-wave potential–pH curves of the β′ and β″ waves, obtained in aqueous solution, indicated that the curves intersect at a lower pH where the order of the two waves is then reversed (Fig. 3*A*). This agrees with the non-formation of formazan in reduction in acid media. The deficiency of this idea lies in that the β wave in the polarogram of triphenyltetrazolium chloride ought to be steepest at the pH of intersection (*i.e.*, about 6) since the potentials of its component β′ and β″ waves only coincide at this point and should diverge above and below it. In the alkaline direction

FIG. 5. *Plot of minimum applied voltage at which formazan is detectable for formazan formation from* 10^{-2}M-*triphenyltetrazolium chloride against* pH.

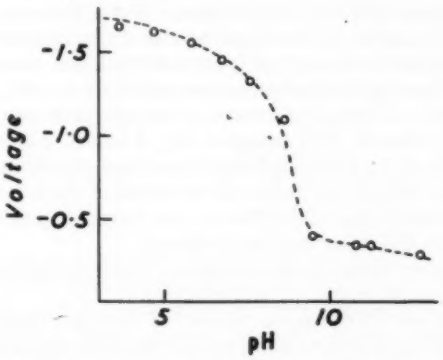
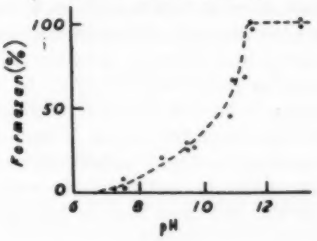


FIG. 6. *Formazan formation* (%) *as a function of* pH *in the macro-electrolytic reduction of triphenyltetrazolium chloride* (10^{-3}M).



the two components do in fact diverge owing to the change in the slope of the half-wave potential–pH curve of the β′ wave. In the acid direction the two components remain fused, as the β′ and β″ waves do not attain sufficient difference in half-wave potential to separate.

That the two half-wave potential–pH curves intersect does not mean that at higher pH's the reduction can only occur *via* formazan and at lower ones by the colourless compound; it means that at this critical point the two routes have equal probability, so that we can assume that a change in pH involves only a change in the probability of route.

In Campbell and Kane's Fig. 4, based on results in 50% methanol, the β wave does not appear to be the resultant of β_1 and β_2, nor does it appear that they intersect as indicated for β′ and β″ by our Fig. 3*A* (for aqueous solution). Comparison of Campbell and Kane's curves and ours for alcoholic solution with ours for aqueous solution shows that the alcohol profoundly changes both the half-wave potential and the character of the curve. Nevertheless it seems very probable that the waves β′ and β″ (for aqueous solution) can be regarded as identical with β_1 and β_2 respectively (for 50% alcohol). We consider results obtained in aqueous solution to be more reliable as a basis for the mechanism.

As has been shown elsewhere,[5] in acid medium formazan fails to form not only in the course of chemical and electrolytic reduction but also during disproportionation caused

[5] Jámbor, *Agrokémia és Talajtan*, 1956, **5**, 89.

by light. In the latter reaction one each of two tetrazolium chloride molecules is oxidised to " photo-tetrazolium chloride ", while the other is mostly reduced to formazan in alkaline medium, and to a water-soluble colourless product in an acid one.

If the latter colourless product is to be prevented from being photo-oxidised *via* triphenyltetrazolium chloride into the photo-compound, the reaction with light must be performed in absence of oxygen. In the polarogram of such a solution a new wave does appear but this cannot be due to the tetrazolium salt or the photo-compound (Fig. 4). Its half-wave potential–pH curve is compared with that of the photo-compound in Fig. 3*A*, and evidence is thus given that in acid medium a colourless reduction product of triphenyltetrazolium chloride exists which is not identical with the formazan. It is oxidised rapidly to the tetrazolium salt in air.

Finally, if triphenyltetrazolium chloride were reduced in acid media by simultaneous uptake of four electrons, no formazan should be formed; benzhydrazyl would have to arise in one step. But precipitation of formazan is observed whenever the light-induced disproportionation or the cathodic reaction is carried out with a sufficiently high concentration of triphenyltetrazolium chloride. This can be understood by remembering that pH changes only alter the probability of the route: if large amounts of the tetrazolium salts are reduced sufficient formazan may be produced to be precipitated and thus not be further reduced.

Jámbor's results [4] and Figs. 5 and 6 bear this out. Fig. 5 shows that a large enough potential difference causes perceptible formation of formazan at the dropping-mercury cathode even at as low a pH as 3, and Fig. 6 shows that application of the same potential causes the amount of formazan of cathodic origin to increase exponentially with pH.

Figs. 5 and 6 do not show the full extent of formazan formation because their course is affected by continued reduction to benzhydrazyl. For example, Fig. 6 indicates that no formazan is formed at pH 6 although half of the total triphenyltetrazolium chloride must have been converted into it. Since at this low pH the half-wave potential of the β'' wave, representing continued reduction, coincides with that of the β' wave, the formazan produced can immediately continue to be reduced to the colourless benzhydrazyl.

All this indicates that in acid medium reduction proceeds through some intermediate other than the formazan.

The question still arises, why the wave of this colourless product of disproportionation by light does not appear on polarograms of triphenyltetrazolium chloride within proper pH limits. If this product were an intermediate product of cathodic reduction of the salt in acid medium, the appearance of this wave could be expected. We did not investigate this question further. It seems probable that the intermediate reduction product of triphenyltetrazolium chloride is not identical with the product of the photo-reaction. It can be assumed that in both cases the reduction occurs *via* the same unknown intermediate, which in cathodic reduction is reduced further at once to benzhydrazyl, and in the case of photo-reduction a secondary rearrangement of this intermediate results in the colourless product, the polarogram of which is shown on Fig. 4.

It is striking that on the polarogram of the tetrazolium salt, in strongly acid medium, the 4-electron wave is followed by another 2-electron wave, which disappears on increase in pH. It is not unlikely that this wave is in some way related to the above colourless reduction product.

Essential to us at the moment is only the fact, for which our data appear to furnish support, that in acid medium the reduction of the tetrazolium salt proceeds not *via* formazan but by way of a colourless reduction product, involving not $N_{(2)}$ and $N_{(3)}$ but $N_{(1)}$ and $N_{(2)}$.

(*c*) We are opposed in principle to Campbell and Kane's basing the mechanism of the reduction on $dE/d(pH)$ values taken from polarograms of methanolic solutions. The Nernst formula is strictly valid only for reversible systems, but reduction of triphenyltetrazolium chloride is only reversible in very alkaline medium, even in respect of its first

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wave. As Campbell and Kane say, the formula can sometimes be applied to irreversible processes, as Jámbor did [2] for aqueous solutions in finding that $dE/d(pH)$ for the β, β″, and β′ wave was 45, 60, and 0 mv respectively, in harmony with the number of protons involved. But for alcoholic solutions the curves are much altered (cf. Figs. 3*A*, *B*, and *C*), so that it is not possible to deduce the number of protons from them. For instance, between pH 8·0 and 8·5 the β_2 curve of Fig. 3*B* breaks upwards sharply, and for the steeply ascending portion the Nernst formula is obviously not valid. Campbell and Kane appear not to have observed this break, perhaps because their pH intervals were too wide, or because they polarographed a solution of higher concentration or, probably, because they used methyl and not ethyl alcohol.

Complications also arise in connection with $dE/d(pH)$ for the β′ wave measured in aqueous medium. Above pH 9 the reduction product should be completely dissociated, and if, as we maintain, it is the formazan, it should be an acid of pK' *ca.* 8, *i.e.*, titratable with alkali. Attempts at such titration failed: the pH of the aqueous alcoholic solution of the formazan was already above 7 before alkali was added and additions of alkali increased the pH of the solution by the same amounts as that of the formazan-free blank.

Accordingly, we maintain that the formazan is not the primary product of the polarographic reduction in alkaline solution, but that it arises from the primary product by a secondary reaction. Jámbor [3,4] showed that the half-wave potential–pH curve of the oxidation wave of the formazan was quite different from that of the corresponding reduction wave: above pH 9 it is not horizontal but has a slope of *ca.* 75 mv/pH unit. Combined with other results, this shows that in the reduction triphenyltetrazolium chloride, using only a small activation energy, first takes up two electrons only, giving the following unstable product:

This intermediate, with liberation of much energy, is converted into the formazan which is more stable than triphenyltetrazolium chloride. The polarogram of triphenyltetrazolium chloride indicates only the primary reaction, the following ring-fission and proton uptake not affecting the β′ wave of the polarogram. Therefore the pK' value indicated by this wave refers to this intermediate, and not to the formazan.

A similar situation may obtain, as we suggested, with the colourless reduction product, and explain why the half-wave potential of the product arising on the action of light differs from that of the intermediate product on the dropping electrode. Further experiments are needed to settle the details of the mechanism of the reduction.

I thank Dr. E. Sándi for carrying out the formazan titrations, and Miss Clara Kisbán for technical assistance.

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321. *Studies in Hydrogen-bond Formation. Part VII.* Reactions between Carbohydrates and Proteins in Water and their Relation to Transfer of Carbohydrates across Red-cell Membranes.*

By I. C. L. Bruce, C. H. Giles, and S. K. Jain.

The refractometric method [1] of detecting intermolecular complexes has been used with dilute aqueous solutions of glucose, sucrose, or *meso*-inositol and proteins or models of proteins. These and other results suggest that: (*a*) normal carbohydrates do not form hydrogen-bond complexes with proteins in dilute aqueous or aqueous alkaline solutions because of the protective effect of the water; and (*b*) *meso*-inositol and simpler solutes, *e.g.*, alcohols, do form complexes, probably by hydrogen-bonding. Differences in transport rates of various solutes including carbohydrates across red-cell membranes can thus be explained. Apparently the more readily the solute forms hydrogen bonds with a protein, the slower is its diffusion rate in the membrane.

Carbohydrates and proteins may react in aqueous media in many biological systems. We have tried to assess the probability of such interactions' being due to hydrogen bonding, which at first appears the most likely mechanism.

Glucose and cellobiose in water form simple complexes [2a] of the same ratio, usually 1 : 1, with several types of nitrogen-containing group in second solutes, but are inactive towards phenols or alcohols. Fructose and sucrose appeared not to form any complex with second solutes in water. The explanation given was that the cyclic forms of these carbohydrates are so strongly hydrogen-bonded to water that no second solute can react with them in aqueous solution. The open-chain form of glucose and cellobiose, however, is apparently less strongly bound to water and can react with certain other solutes through its aldehyde group; the hydroxy-groups remain inactive, probably through weak chelation (cf. the chelation of polyhydric alcohols [2a]). Fructose or sucrose cannot react even as the open-chain molecule, because the end-group in that form, *viz.* the keto-group, is itself unreactive in water.

Several authors have examined the reactions of carbohydrates with proteins. Some complexes appear to be formed in water, but only in fairly concentrated solutions.[3-5] There is evidence, for example, that under alkaline conditions some carbohydrates, but not sucrose, interact with amino-groups in proteins,[3,4] but the products are unstable under biological conditions.[4] It seems likely that only when the solutions are concentrated can the carbohydrate–protein attraction break down the barrier of solvated water and lead to formation of complexes.

We examined refractometrically three proteins (casein, edestin, and gelatin) and several models for the polar groups in proteins [*N*-methylacetamide, glycine, dimethylformamide, diacetamidomethane (cf. ref. 2*b*), ethylamine, and propionic acid]. Since glucose and cellobiose behave as aldehydes in water,[2a] a few tests were made with simple aldehydes. *meso*-Inositol was included for comparison with the normal carbohydrates, because of its different biological properties.

* Part VI, *J. Soc. Dyers and Colourists*, in the press; Part V, Arshid, Giles, and Jain, *J.*, 1956, 1272.

[1] Arshid, Giles, McLure, Ogilvie, and Rose, *J.*, 1955, 67.

[2] (*a*) Arshid, Giles, and Jain, *J.*, 1956, 559 (in Table 1 of this paper the mol. ratio of the D-cellobiose–aniline complex *should read* 2 : 1. On p. 569, first line, *for* free acid *read* no free acid); (*b*) Arshid, Giles, Jain, and Hassan, *J.*, 1956, 72.

[3] Przylecki, *Acta Biol. Exptl.* (*Warsaw*), 1938, **12**, 82; *Chem. Abs.*, 1939, **33**, 6351.

[4] Przylecki and Cichocka, *Biochem. Z.*, 1938, **299**, 92.

[5] Haurowitz, "Chemistry and Biology of Proteins," Academic Press Inc., New York, 1950.

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Experimental

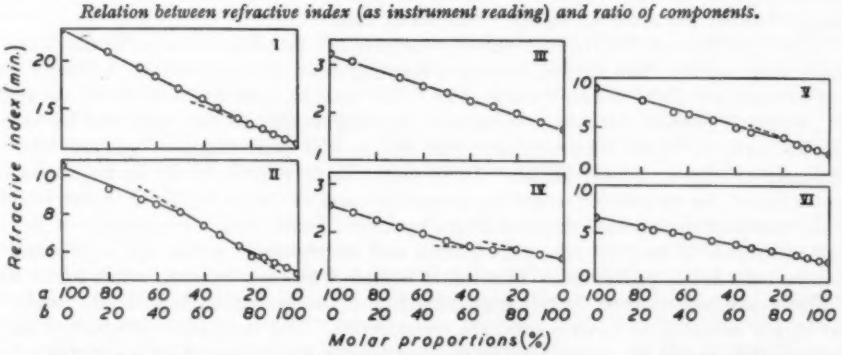
Full details of the method and the general significance of the results have been given.[1] Distilled water was used as solvent. Casein (" light white soluble ") and edestin were obtained from British Drug Houses Ltd.; gelatin was of pure photographic quality; other reagents including sodium chloride were " AnalaR " or were purified by normal methods. A Pulfrich

Results of complex-detection tests.

Solute *a*	Concn. (M)	Solute *b*	Concn.*	Solvent †	Mol. ratio of complex, *a* : *b* ‡
Acetaldehyde	0·5	*N*-Methylacetamide	0·5M	W	0
	0·5	Dimethylformamide	0·5M	W	(1 : 1)
	0·5	Diacetamidomethane	0·5M	W	0
	0·5	Propionic acid	0·5M	W	0
*iso*Butyraldehyde	0·5	*N*-Methylacetamide	0·5M	W	0
Terephthaldehyde	0·1	*N*-Methylacetamide	0·1M	WEl	0
	0·1	Dimethylformamide	0·1M	WEl	0
D-Glucose	0·01	Casein	1·25 g./l.	B9	0
	0·0085	Edestin	1·07 g./l.	S	0
	0·1	Gelatin	10·6 g./l.	W	0
	0·1	Glycine	0·1M	W	0
	0·5	*N*-Methylacetamide	0·5M	W	0
	0·5	Ethylamine	0·5M	W	1 : 1
Sucrose	0·1	*N*-Methylacetamide	0·1M	W	0
	0·01	Casein	1·25 g./l.	B9	0
meso-Inositol	0·1	*N*-Methylacetamide	0·1M	W	1 : 3
	0·1	*p*-Cresol	0·1M	W	(1 : 1); 1 : 3
	0·1	Phenol	0·1M	W	1 : 1; 1 : 3
	0·01	Casein	1·25 g./l.	B9	0
	0·0085	Edestin	1·07 g./l.	S	See Fig.
	0·1	Gelatin	10·6 g./l.	W	See Fig.

* Weights of proteins refer to the normal air-dry condition.
† Solvents: B9 = pH 9·0 Buffer solution; S = 1·0M aqueous sodium hydroxide solution; W = water: WEl = 50% (v/v) aqueous ethanol.
‡ Data in parentheses denote uncertain indications; 0 denotes no evidence of complex formation.

Relation between refractive index (as instrument reading) and ratio of components.



Solvent: water
I: *a*, *meso*-Inositol; *b*, *N*-methylacetamide.
II: *a*, *meso*-Inositol; *b*, phenol.

Solvent: 1·0M-NaOH soln.
III: *a*, D-Glucose; *b*, edestin.
IV: *a*, *meso*-Inositol; *b*, edestin.

Solvent: water
V: *a*, *meso*-Inositol; *b*, **gelatin.**
VI: *a*, Glucose; *b*, gelatin.

refractometer (Bellingham and Stanley), on which an experienced operator's standard deviation was about 3·5 sec., was used with sodium light, all measurements being made at room temperature; the mixed solutions containing proteins were kept overnight before being tested.

Casein was dissolved in pH 9 buffer, edestin in 1·0M sodium hydroxide solution, and gelatin in water, the second solutes in each case being dissolved in the same respective liquid. The

refractive indices are proportional to concentration and additive, and the theory of the method [1] shows that the two solutions need not be of the same molarity, although if they are not, any complex-ratio shown in the graphs must be adjusted.

Results and Discussion

The results (Table and Figure) give no evidence that hydrogen-bond interaction in dilute aqueous solution can take place between normal carbohydrates and proteins, but they suggest that it may occur between inositol and proteins.

The aldehydes, including glucose, react in 1 : 1-ratio with several simple model compounds, *e.g.*, dimethylformamide, triethylamine, pyridine, etc.,[2a] but, surprisingly, none gives any evidence of reaction with the $-CO\cdot NH-$ group in *N*-methylacetamide or with the peptide link in casein, or reacts with aliphatic carboxylic acids. Aldehydes and glucose react with amino-groups (cf. ref. 2*a*), but we obtained no evidence that they do so with the side-chain amino-groups in proteins in alkaline or neutral solution, probably because under such conditions these groups are either in the zwitterion form or bound in covalent salt links. Sucrose was known not to react with several other solutes,[2a] and now appears unreactive towards *N*-methylacetamide or casein. Apparently, adsorption from dilute aqueous solutions of carbohydrate to protein or *vice-versa* can take place only by non-polar van der Waals forces.

Inositol (hexahydroxy*cyclo*hexane), unlike other carbohydrates, does form complexes with the phenolic and amide groups and with edestin and gelatin in water. The difference must reflect the relative affinity of the two types of compound for water (cf. water solubility: *meso*-inositol, 4·5; D-glucose, 83 g., per 100 c.c. of water at 15° and 17·5° respectively). Inositol is therefore less firmly bound to the solvent and its solvated water can more readily be replaced by another solute molecule.

We cannot suggest possible modes of attachment of inositol to the proteins; about one molecule appears to be combined for every 5 amino-acid residues in gelatin and for every 1·5 or 4 in edestin, for which there is evidence of two different complexes (Figure), the average molecular weight per residue in gelatin [6] being taken as about 75 and in edestin [5] about 105 (that for casein [5, 6a] is about 105).

Stein and Danielli [7] state that sugars penetrate cell membranes in particular instances much more rapidly than simpler hydrogen-bonding molecules, *e.g.*, water, methanol, urea, and formamide; Bowyer and Widdas state [8] that *meso*-inositol differs from normal sugars, *viz.*, fructose, glucose, sorbose, and sucrose, in being unable to penetrate red blood cells. Various authors [8] have observed also that the rate of penetration of glucose into cells decreases at higher concentrations. These facts can be related to the hydrogen-bonding properties of the solutes concerned by a consideration of the present and earlier results.[2a] If the solute in an aqueous medium forms hydrogen bonds with a component of the cell-wall membrane it may be adsorbed thereto and its transport across the membrane will then be retarded or prevented. This would explain why *meso*-inositol, which forms bonds in dilute aqueous solution, is not transported, and the normal carbohydrates, which are too highly solvated to form bonds, are transported. The decreased penetration rate of glucose with rise in its concentration in solution can be explained by an increase in its ability to form hydrogen bonds with the solid subtrate when the protective effect of the solvent becomes less pronounced.

Bowyer and Widdas consider that the penetration of sugars into human red cells is not a simple diffusion and probably first requires the formation of a complex between the sugar and some (unidentified) membrane component; we suggest that this complex appears to be formed by non-polar forces. Bowyer and Widdas suggest that the hexose-transfer

[6] (*a*) Traill, *J. Soc. Dyers and Colourists*, 1951, **67**, 257; (*b*) Eastoe, *Biochem. J.*, 1955, **61**, 589.
[7] Stein and Danielli, *Discuss. Faraday Soc.*, 1956, **21**, 238.
[8] Cf. Bowyer and Widdas, *Discuss. Faraday Soc.*, 1956, **21**, 251.

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system is of wide biological significance, occurring as it does not only in human red cells, but in other species and tissues.

We thank Professor P. D. Ritchie for his interest, Mr. R. B. Collins and Ilford Ltd. for a sample of pure gelatin, Dr. J. C. P. Schwarz for a sample of *meso*-inositol, Mr. T. H. MacEwan for experimental assistance, and Imperial Chemical Industries Limited, Central Research Department, for a grant for equipment.

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[*Received, September 13th*, 1957.]

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322. *Calculations of the Crystal Spectra of Benzene and Naphthalene.*

By D. P. Craig and J. R. Walsh.

An E_{1u} state of benzene is split in the crystal into four components, three of them spectrally active. The splittings and intensity distribution for transitions to them are calculated according to perturbation theory by using methods discussed in earlier papers and now adapted to deal with a twofold degenerate upper state. Dipole sums have been found by two independent methods in good agreement with one another.

Calculations are reported for crystal transitions in naphthalene corresponding to band systems observed in solution at 2200 Å and 2750 Å. Their assignments as long-axis and short-axis polarised respectively are confirmed by comparison of the calculated results with experiment and by analogy with anthracene.

1. Molecules in crystals interact with forces which are small compared with intramolecular forces and accordingly the energy levels of crystals can be calculated from, and uniquely related to, those of free molecules by perturbation theory. A number of such studies have been made, beginning with Davydov's theoretical work [1] and including, for example, the weak A_g–B_{2u} system of benzene [2] and two transitions of anthracene.[3,4] Calculations are now reported for the intense system of benzene at 1790 and for two systems of naphthalene, at 2200 Å and 2750 Å. The crystal spectrum corresponding to the intense benzene system has not hitherto been discussed theoretically; our naphthalene results have already been briefly reported.[5]

We first restate the theory used briefly. It is derived so far as symmetry is concerned mostly from Seitz [6] and in other respects from Davydov and other authors already cited. A molecule will be supposed to have a ground state wave-function φ and a set of excited states φ^r. The transitions in the free molecules from the ground state have transition energies Δw^r measured in the equivalent wave numbers and transition dipole moments $\boldsymbol{M}^r = e\boldsymbol{Q}^r$ with the dipole lengths measured in Ångström units. In the crystal there will be h such molecules in a unit cell each occupying a *site* designated by a subscript $i = 1, 2, \ldots h$, and if the crystal consists of N molecules there will be N/h unit cells numbered by a second subscript $m = 1, \ldots N/h$. Thus the symbol $\varphi_{lm}{}^s$ refers to a molecule in its s-th excited state placed on the l-th site of the m-th unit cell. Where specification of the unit

[1] Davydov, *Zhur. eksp. teor. Fiz.*, 1948, **18**, 210.
[2] Fox and Schnepp, *J. Chem. Phys.*, 1955, **23**, 767.
[3] Craig and Hobbins, *J.*, 1955, 539, 2309.
[4] Craig, *J.*, 1955, 2302.
[5] Craig and Walsh, *J. Chem. Phys.*, 1956, **24**, 471; **25**, 588.
[6] Seitz, *Ann. Math.*, 1936, **37**, 17.

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cell is unnecessary the second subscript is omitted. The Hamiltonian for the rigid lattice may be written

$$\sum_{k=1}^{N} \left(\mathbf{H}_k + \sum_{l>k} \mathbf{V}_{lk} \right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

in which $\mathbf{H}_k$ is the Hamiltonian for the k-th molecule in isolation and $\boldsymbol{V}_{lk}$ is the interaction energy between the molecules k and l. Writing the crystal ground state wave function as a simple product of free molecule functions (2)

$$\Phi_G = \varphi_1 \varphi_2 \cdots \varphi_N \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

we find for the energy to the first order the expression (3):

$$E_G = Nw + \sum\sum \int \varphi_l \varphi_k \mathbf{V}_{lk} \varphi_l \varphi_k \mathrm{d}\tau \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Excitation of the p-th molecule of the i-th set to its r-th excited state is represented in a localised excitation wave function (4):

$$\phi_{ip}{}^r = \varphi_{11} \varphi_{12} \cdots \varphi_{ip}{}^r \cdots \varphi_{h,N/h} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

If all molecules are of one crystallographic species this belongs to an N-fold degenerate set with respect to the N-excitation sites: the overall degeneracy is the product of this site degeneracy and that of the molecule wave function. Where there is more than one crystallographic species the degeneracy of the functions (4) extends to the members of each species but not, of course, outside it. Approximate eigenfunctions for excited states of the crystal are linear combinations of the localised excitation functions (4), and the problem of finding the coefficients for them can always be partly solved, and sometimes completely, by using symmetry arguments.

2. *Symmetry Considerations.*—The Hamiltonian (1) is invariant under the operations of the space group and the setting up of crystal wave functions is simplified by making them transform like irreducible representations. The infinite crystal is simulated by applying cyclic boundary conditions to the finite crystal of N molecules, the group of which is the finite space group of Winston and Halford.[7] This contains as an invariant sub-group the finite translation group consisting of the lattice translations (5):

$$n_1 \mathbf{t}_1 + n_2 \mathbf{t}_2 + n_3 \mathbf{t}_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where the $\mathbf{t}$'s are primitive lattice vectors and the n's integers which, in (5), generate from a chosen molecule a set of molecules translationally equivalent to it.

Using the functions (4), we now set up normalised linear combinations (6) of translationally equivalent molecules with irreducible symmetry under the translation group:

$$\Phi_i{}^r(\mathbf{k}) = \sqrt{(h/N)} \sum_{ip} \exp\left(i\mathbf{k} \cdot \mathbf{r}_{ip}\right) \phi_{ip}{}^r \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

$\mathbf{r}_{ip}$ is the position vector of the p-th molecule of the i-th set, and $\mathbf{k}$ is a wave vector; $\mathbf{k}$ may be regarded as a vector in reciprocal space. Its components along the three crystal axes a, b, and c are limited, for example, along a, to $2\pi\sigma/(M_a \cdot a)$ for $\sigma = 0, \pm 1, \pm 2, \ldots M_a/2$ where a is the lattice spacing and M_a the number of translationally equivalent molecules along the a axis; $M_a M_b M_c = N/h$.

The invariant sub-group of translations is associated in the space group with the factor group or unit-cell group, and reference will be made also to two other groups, namely the site group and the group of the wave vector $\mathbf{k}$. The factor group consists of operations which leave the Hamiltonian for the molecules in a unit cell unchanged, either by interchanging the molecules or by mapping them on themselves or their translational

[7] Winston and Halford, *J. Chem. Phys.*, 1949, **17**, 607.

equivalents. In the most general case each factor-group operation carries a chosen molecule into another crystallographically equivalent to it. Then, if all the molecules in the unit cell are crystallographically equivalent the order of the factor group equals the number of molecules in the unit cell.* In this case the site group, which consists of those factor-group operations which leave the Hamiltonian for one molecule unchanged, contains only the identity. In more special cases some factor-group operations permute the molecule Hamiltonians $\mathbf{H}_k$ while others leave them invariant; the latter operations constitute the site group. The number of molecules in the unit cell then equals the number of operations effecting distinct permutations in the factor group plus one, *i.e.*, its order divided by the order of the site group. Thus, in the naphthalene crystal there are two molecules per cell and the factor group C_{2h} is of order four. The identity and inversion operations self-transform the molecules, giving a site group C_i of order two.

To describe the group of the wave vector we must consider the transforms of the functions (6) by a factor-group operation $\mathbf{F}$. In accordance with what has just been said, let us suppose that $\mathbf{F}$ carries a molecule of the i-th translationally equivalent set into the j-th and the p-th unit cell into the q-th. Then

$$\mathbf{F}\Phi_i^r(\mathbf{k}) = \sqrt{(h/N)} \sum_q \exp(i\mathbf{k} \cdot \mathbf{r}_{jq})\, \phi_{jq}^r \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

This is identical with the result of the operation $\mathbf{F}$ applied to the vector $\mathbf{k}$, the $\mathbf{r}$ vectors being altered only to apply to the new site:

$$\mathbf{F}\Phi_i^r(\mathbf{k}) = \Phi_j^r(\mathbf{Fk}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Thus the factor-group operations generate a set of wave vectors from a chosen $\mathbf{k}$. This set, radiating from a point of reciprocal space, is called a star by Wigner *et al.*[8] In general each factor-group operation generates a different $\mathbf{Fk}$ and, even if inversion of space coordinates is not a factor-group operation the negative of each wave vector is included in the star as a result of symmetry to time inversion. Thus the most general star consists of as many vectors as there are factor-group operations, or twice as many, depending upon whether space inversion is, or is not, an element of the factor group. In special cases the wave vector $\mathbf{k}$ is invariant to certain of the factor-group operations; these constitute a sub-group called the group of the wave vector. The functions (6) which transform like the $\mathbf{k}$ representation of the translation group can in addition be combined to transform like representations of the group of the wave vector. In the case $\mathbf{k} = 0$ the wave vectors on the left- and the right-hand side of (8) are the same, so the group of the wave vector is the point group isomorphous with the whole factor group, and crystal wave functions can be classified according to factor-group representations. This is of prime importance for optical transitions which are mainly to states of $\mathbf{k} = 0$. On the other hand, for the most general $\mathbf{k}$ the group of the wave vector consists only of the identity and time inversion and no subclassification of the functions (6) can be made.

The energy levels of the crystal are found by diagonalising the energy matrix of the Hamiltonian (1) in the basis of functions (6). It is somewhat more convenient to calculate directly the transition energies by subtracting the ground-state energy (3). The required transition energies to the first order can be found from the secular equation (9):

$$det\left\{[\Phi_i^r(\mathbf{k})|\sum \mathbf{H}_k + \sum\sum \mathbf{V}_{kl} - E_G|\Phi_j^r(\mathbf{k})] - [\Phi_i^r(\mathbf{k})|1|\Phi_j^r(\mathbf{k})]E\right\} = 0 \quad . \quad (9)$$

* Where the unit cell contains more than one crystallographically distinct molecule each is considered separately in the same way under the factor-group operations.

[8] Bouckaert, Smoluchowski, and Wigner, *Phys. Rev.*, 1936, **50**, 58.

and to higher order of approximation by including in the basis functions corresponding to different free-molecule excited states as discussed in ref. 4. In the diagonal places in the determinant we find

$$\Delta w^r + D^r + \sum_q{}' \exp[i\mathbf{k} \cdot (\mathbf{r}_{ip} - \mathbf{r}_{iq})] I_{ip,iq}{}^{rr} - \Delta E \quad . \quad . \quad . \quad . \quad (10a)$$

and in the non-diagonal

$$\sum_q (\exp[i\mathbf{k} \cdot (\mathbf{r}_{ip} - \mathbf{r}_{jq})] I_{ip,jq}{}^{rr} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10b)$$

where

$$D^r = \sum_q{}' \left\{ (\varphi_p{}^r \varphi_q | \mathbf{V}_{pq} | \varphi_p{}^r \varphi_p) - (\varphi_p \varphi_q | \mathbf{V}_{pq} | \varphi_p \varphi_q) \right\}$$

$$I_{ip,jq}{}^{rr} = (\varphi_{ip}{}^r \varphi_{ip} | \mathbf{V}_{ip,jq} | \varphi_{jq}{}^r \varphi_{jq})$$

and the primed sums omit $p = q$. The degree of the secular equation is equal to the number of molecules in the unit cell but it can be factorised into smaller blocks by using the group of the wave vector and, in the case $\mathbf{k} = 0$, using the factor group.

3. *Application to Benzene.*—Benzene crystals are orthorhombic with four molecules in the unit cell. These will be numbered as follows: I is at (0, 0, 0) and the others are generated from it by applying the factor-group operations as defined in Table 1. A set of rectangular axes is assigned to I: the z axis is normal to the molecular plane with its positive direction making acute angles with the positive directions of the crystal axes a, b, and c; the y axis is the intersection of the molecular plane with the ab crystal plane with positive direction making an acute angle with the positive b axis, and the x axis is perpendicular to y and z and makes acute angles with a and b but not c. The axes in the other molecules are the transforms of those in I by the factor-group operations. Table 1 sets out the direction cosines of molecular to crystal axes derived in this way from the results of Cox and Smith.[9]

TABLE 1. *Direction cosines of molecular axes with respect to crystal axes in benzene crystals.*

Molecular type	Method of generation	Crystal axes	Direction cosines x	y	z
I	E	a	0·6365	−0·2992	0·7109
		b	0·2000	0·9541	0·2229
		c	−0·7450	0	0·6671
II	$C_2{}^a$	a	−0·6365	0·2992	−0·7109
		b	−0·2000	−0·9541	−0·2229
		c	−0·7450	0	0·6671
III	C_2	a	−0·6365	0·2992	−0·7109
		b	0·2000	0·9541	0·2229
		c	0·7450	0	−0·6671
IV	$C_2{}^a$	a	0·6365	−0·2992	0·7109
		b	−0·2000	−0·9541	−0·2229
		c	0·7450	0	−0·6671

For the calculation of optical transitions the energy levels belonging to $\mathbf{k} = 0$ are the important ones. The corresponding wave functions transform like representations of the factor group, as explained in the last section, and are given in the basis of the functions (4) by the following expressions (11):

$$\gamma^\alpha = (1/2)(\phi_{\mathrm{I}}{}^r + \phi_{\mathrm{II}}{}^r + \phi_{\mathrm{III}}{}^r + \phi_{\mathrm{IV}}{}^r)$$
$$= (++++)$$
$$\gamma^\beta = (+-+-)\ \gamma^\delta = (+--+)\ \gamma^\epsilon = (++--) \quad . \quad . \quad . \quad ((11)$$

The functions γ transform under the twofold rotations in the same way for any molecular state φ^r and, because the site group contains inversion, the g or u character is the same as

[9] Cox and Smith, *Nature*, 1954, **173**, 75.

that of the molecule wave function. The complete crystal wave functions for $\mathbf{k} = 0$ are sums of the expressions γ over all unit cells. The factor-group representations for a molecular u wave function are set out in Table 2.

TABLE 2. *Factor-group representations and polarisations for crystalline benzene* ($\mathbf{k} = 0$).

Wave function	D_{2h} representation	Transition dipole direction (Forbidden)
γ^α	A_{1u}	
γ^β	B_{2u}	b
γ^δ	B_{1u}	a
γ^ϵ	B_{3u}	c

The transitions referred to are from the ground state which is g, and there are no allowed transitions leading to excited states of the crystal corresponding to g excited molecular states. For a non-degenerate molecular wave function φ^r there is just one crystal wave function belonging to each factor-group representation, but for a doubly degenerate molecule wave function there will be two, and these two will be split by the crystal field as we shall see for the E_{1u} state of benzene.

The energies of the crystal levels relative to those of free molecules depend, at least when the levels give rise to intense absorption systems, on resonance effects between molecules. These have been discussed in Section 1 and more fully in refs. 1 and 3. For $\mathbf{k} = 0$ the magnitudes depend on sums of integrals of the intermolecular potential energy $\mathbf{V}_{kl}$ between all molecule pairs kl. The symmetry relations in Table 1 reduce the integrals to a small number of different types each involving a selected molecule which we choose to be a member of the set translationally equivalent to I. Written in full a representative integral sum is (12):

$$\sum_{j=1}^{N/4} I_{\mathrm{I}l,j\mathrm{K}}{}^{xx} = \sum_j (\varphi_{\mathrm{I}l}{}^x \varphi_{\mathrm{I}l} | \mathbf{V}_{\mathrm{I}l,j\mathrm{K}} | \varphi_{j\mathrm{K}}{}^x \varphi_{j\mathrm{K}}) \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

The superscripts refer to the x component of the degenerate excited state φ^r as will be explained later. The integral sums occur in combinations determined by the appearance of the functions ϕ in (11) and defined below; the expressions are simplified by giving only that subscript which refers to the set of molecules over which the sum is taken.

$$\left.\begin{aligned} \mathscr{J}_\alpha{}^{xx} &= \sum I_{\mathrm{I}}{}^{xx} + \sum I_{\mathrm{II}}{}^{xx} + \sum I_{\mathrm{III}}{}^{xx} + \sum I_{\mathrm{IV}}{}^{xx} \\ \mathscr{J}_\alpha{}^{xy} &= \sum I_{\mathrm{I}}{}^{xy} + \sum I_{\mathrm{II}}{}^{xy} + \sum I_{\mathrm{III}}{}^{xy} + \sum I_{\mathrm{IV}}{}^{xy} \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad 13$$

Analogous combinations occur in the energies of, and have the same sequences of signs as, the wave functions specified by subscripts β, δ, and ϵ.

For the doubly degenerate E_{1u} state of benzene there are two primitive crystal wave functions of each factor-group representation, and hence two distinct crystal energy levels, found by diagonalising a two-rowed secular equation. The elements of the four such secular equations are formally the same. For the A_{1u} factor group representation for example:

$$\begin{vmatrix} \mathscr{E} + \mathscr{J}_\alpha{}^{xx} & \mathscr{J}_\alpha{}^{xy} \\ \mathscr{J}_\alpha{}^{yx} & \mathscr{E} + \mathscr{J}_\alpha{}^{yy} \end{vmatrix} = 0 \qquad \mathscr{E} = \Delta w^r + D - \Delta E$$

For the mean energy displacement from a reference zero equal to $\Delta w^r + D$ we have $(1/2)(\mathscr{J}^{xx} + \mathscr{J}^{yy})$, and the two components are each separated from this by

$$(1/2)\left\{(\mathscr{J}^{xx} - \mathscr{J}^{yy})^2 + 4(\mathscr{J}^{xy})^2\right\}^{1/2}$$

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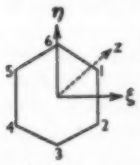
In the dipole–dipole approximation [3] the expression for a representative term occurring in the sum $\mathcal{J}^{xy}$ is as follows, for molecules l and m:

$$-(1/2)(1/r_{lm}^3)|\boldsymbol{M}^x||\boldsymbol{M}^y|\{2\cos\theta_{l1}^x\cos\theta_{m1}^y + 2\cos\theta_{l1}^y\cos\theta_{m1}^x - \cos\theta_{l2}^x\cos\theta_{m2}^y - \cos\theta_{l3}^x\cos\theta_{m3}^y - \cos\theta_{l2}^y\cos\theta_{m2}^x - \cos\theta_{l3}^y\cos\theta_{m3}^x\} . \quad (14)$$

r_{lm} is the distance between the centres of the molecules, $\boldsymbol{M}^x$ is the transition dipole moment for the transition to φ^x, and θ_{l1}^x is the angle between the transition moment and the line of centres of the molecules. Axes 2 and 3 are perpendicular to the line of centres.

We must now consider the transition moments for the free molecule. It is well known that an E_{1u} wave function in group $\boldsymbol{D}_{6h}$ can be expressed in two orthogonal functions which depend on the angle round the z axis according to the sine and cosine of $2\pi k/6$ when k numbers the vertices of the hexagon from 1 to 6. With the numbering in the diagram



the transition dipole moments from the ground state lie respectively along the η and ξ directions for the sine- and cosine-dependent functions. By taking general linear combinations in terms of an angle parameter χ, we get two orthogonal functions with angle dependence given by $(\cos\chi\,.\cos 2\pi k/6 + \sin\chi\,.\sin 2\pi k/6)$ and $(-\sin\chi\,.\cos 2\pi k/6 + \cos\chi\,.\sin 2\pi k/6)$, the transition dipoles for which are rotated through χ from those for the original. Thus in an isolated molecule the transition moment to the degenerate E_{1u} state can be regarded as having components along any two axes at right angles in the molecular plane. We shall take the wave-function component φ^y to be that which has its transition dipole moment along the line of intersection of the molecular plane with the *ab* plane of the crystal, *i.e.*, the y axis already defined, and φ^x similarly.

The first stage of the numerical work is the computation of the dipole–dipole sums, given in Table 3 for a transition dipole length of 1 Å. Values in the Table have been computed in two distinct ways. The results marked (*a*) are sums over an infinite sphere by the Ewald–Kornfeld [10] method, and (*b*) are obtained by direct molecule-by-molecule evaluation over a sphere of radius 20 Å. We discuss and compare these methods of evalu-

TABLE 3. *Benzene crystal dipole–dipole sums* (cm.$^{-1}$/Q^2).

Dipole axes		Molecule sites I, I	I, II	I, III	I, IV	Dipole axes		Molecule sites I, I	I, II	I, III	I, IV
(*x*, *x*)	(*a*)	−386	−112	−791	−729	(*x*, *y*)	(*a*)	205	−947	−25	275
	(*b*)	−415	− 92	−769	−771		(*b*)	233	−934	− 8	289
(*y*, *y*)	(*a*)	727	−2679	−1723	1341	(*x*, *z*)	(*a*)	207	1340	−738	795
	(*b*)	790	−2629	−1713	1405		(*b*)	181	1306	−818	833
(*z*, *z*)	(*a*)	−341	185	−955	−553	(*y*, *z*)	(*a*)	228	−1058	−27	307
	(*b*)	−375	220	−950	−587		(*b*)	260	−1041	− 7	323

ation later. The sums (*a*) are used in the calculations of the crystal energy levels given in Table 4. These are characterised by the displacement of each level from a zero given by $\Delta w^r + D$ which is expected to be close to the free-molecule excitation energy. There are two levels belonging to each symmetry species labelled (i) and (ii), separated by an amount which measures the degree to which the crystal field splits the free-molecule degeneracy in the several symmetries.

The transition intensities in the crystal are conveniently considered in two steps: first, the sharing of the total intensity between the three axes of polarisation, and secondly,

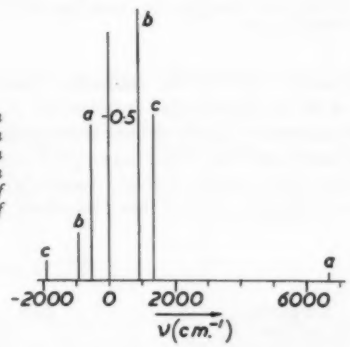
[10] Kittel, " Introduction to Solid State Physics," John Wiley, New York, 2nd edn., 1954, p. 347.

the subdivision between the two components polarised along each axis. In first-order theory the partition between the three axes is determined by their projections on the active molecular axes. Denoting the transition dipole length projected along the crystal axes by Q_a, Q_b, and Q_c, we find that the squares of these quantities are in the ratios 1 : 1·92 : 1·12. If the splittings are taken to be small compared with the transition energy Δw^r, these are also the ratios of oscillator strengths along the axes. To determine absolute intensities

TABLE 4. *Calculated positions of crystal levels of benzene for* $\mathbf{k} = 0$ *relative to* $\Delta w^r + D$ (cm.$^{-1}$/Q^2).

$\alpha(A_{1u})$	$\beta(B_{2u})$	$\delta(B_{1u})$	(B_{2u})	$\alpha(A_{1u})$	$\beta(B_{2u})$	$\delta(B_{1u})$	(B_{2u})
−2693	−914	−514	−1906	−1659	+920	+6772	+1358

we use the formula for f, the oscillator strength, $f = A \,.\, \Delta E \,.\, Q^2$, where ΔE is the transition energy in Rydberg units, Q the transition dipole length in atomic units, and A the square of the cosine of the angle between Q and the polarisation direction of the incident light. In solution, A averages at 1/3; in the crystal it can be found from Table 1. The total f value summed over the three axes is evidently three times the solution value.



The calculated structure of the crystal spectrum corresponding to a vapour A_{1g}–E_{1u} *system of benzene, showing splittings, polarisation directions and transition dipole lengths in* Å. *The values apply to a transition of intensity with dipole length* 1Å *in each of the two degenerate components.*

The partition of these intensities between the two components along each axis can be determined from the solutions of the two-rowed secular equations (13) which give the coefficients for the mixing of φ^x and φ^y in the crystal eigenfunctions. The results are expressed as the ratios of the squares of transition moments. The values found (the higher frequency first) are: *a* polarised 0·057 : 1; *b* 5·94 : 1; *c* 8·72 : 1. The Figure illustrates the results, showing the splittings and intensity distribution in an intense A_{1g}–E_{1u} system. The frequency zero is $\Delta w^r + D$.

We have discussed the influence of crystal forces on the degenerate E_{1u} state of benzene without referring to Jahn and Teller's theorem [11] which shows that electronic degeneracy and a non-linear nuclear arrangement are incompatible. According to Jahn and Teller the regular hexagonal shape of a free benzene molecule must collapse in a degenerate state into an elongated hexagon with dimensions governed by the balance reached between σ-electron forces tending to preserve regularity and π-electron forces opposing it. In the crystal we treat the levels appropriate to molecules in which the regular hexagon is preserved, for the following reason. The degeneracy having been removed by crystal forces even in the regular shape, there will be no first-order Jahn–Teller effect, and its vestigial influence on shape will be of the same order as that of the crystal forces themselves and therefore properly to be neglected in the present approximation, the essence of which is that the time constant for nuclear displacements is long compare with that for

[11] Jahn and Teller, *Proc. Roy. Soc.*, 1937, *A*, **161**, 220.

exciton transfer; this being so, the crystal levels are predominantly determined by the molecular dimensions in the ground state.

4. *Application to Naphthalene.*—The considerations of molecule and crystal symmetry for naphthalene are identical with those for anthracene already given in detail.[3] Moreover, calculations for naphthalene have already been reported briefly and will here only be summarised. The space group is C_{2h}^5 with two molecules in the unit cell; for each $\mathbf{k}$ value a free molecule state gives rise to two crystal levels. For $\mathbf{k} = 0$ transitions are allowed to both components of a u state, polarised in the one case in the ac plane and in the other along the b axis. Since naphthalene crystallises with a prominent (001) plane, measurements are made along the a and b monoclinic axes. Their energies may be calculated in relation to the free-molecule transition energy by using the intermolecular integral sums given in Table 5, computed in the dipole–dipole approximation. The in-plane transitions

TABLE 5.* *Naphthalene crystal dipole sums* (cm.$^{-1}/Q^2$).

Dipole axes	Molecule sites I, I	I, II	Dipole axes	Molecule sites I, I	I, II	Dipole axes	Molecule sites I, I	I, II
(y, y)	(a) 555	(a) 1350	(z, z)	(a) −789	(a) 84	(y, z)	(a) 323	(a) 1160
	(b) 581	(b) 1450		(b) −854	(b) 90		(b) 366	(b) 1164

* Calculations based on the crystal structure reported by Abrahams, Robertson, and White, *Acta Cryst.*, 1949, **2**, 238.

in naphthalene have their moments parallel to the longer in-plane axis (y-polarised A_g–B_{2u}) or along the shorter (z-polarised A_g–B_{1u}) in the recommended convention.[12] The left-hand column of Table 5 lists the combinations of transition moment directions in the two molecules, and the sums taken over equivalent and non-equivalent molecule pairs are given in the right-hand columns; values labelled (a) are Ewald–Kornfeld (EK) sums taken over the infinite sphere, and those labelled (b) are direct sums (DS) over a 20 Å sphere.

TABLE 6.*

Assignment	$\Delta E\alpha$ (cm.$^{-1}$)	$\Delta E\beta$	Splitting $\Delta E\alpha - \Delta E\beta$	Shift $(\Delta E\alpha + \Delta E\beta)/2$
Long-axis (y) poln. A_g–B_{2u}	+6570	−2740	+9310	+1910
Short-axis (z) poln. A_g–B_{1u}	−2430	−3010	+580	−2720

* The minor differences between these results and those given in reference (5) are due to the substitution of EK values for the slightly different DS ones.

Naphthalene has three known singlet band systems in the quartz ultraviolet region, at 2200 Å ($f = 1{\cdot}7$), at 2750 Å ($f = 0{\cdot}11$), and at 3200 Å ($f = 0{\cdot}002$), of which the last is too weak to be treated in the dipole–dipole approximation. Table 6 refers to the first of the three systems and gives values of the Davydov splitting and shift based on the EK values in Table 5 and measured relative to $\Delta w + D$ as in expression (10a). The superscripts α and β refer respectively to a and b polarised absorption. Experimental evidence to determine the polarisation of this system is not available but analogy with the strongly similar anthracene absorption system and indirect evidence to be discussed based on the influence of the strong system on the weaker one at 2750 Å make it evident that the 2200 Å system is long-axis polarised.

In the weaker system at 2750 Å there are two features of the crystal spectrum not found in strong systems, again as in the similar system of anthracene at 3800 Å. The transition dipole length calculated from the observed oscillator strength in solution is 0·53 Å, so that the Davydov splitting will not exceed 400 cm.$^{-1}$ whatever the assignment. This is substantially smaller than the vibrational spacing of the progression, so that one cannot treat the electronic intensity as concentrated at one frequency but must consider each vibrational-electronic level of the progression separately. When the splitting energy

[12] Report of Joint Commission for Spectroscopy, *J. Chem. Phys.*, 1955, **23**, 1997.

is small compared with the progression interval, the splitting actually observed depends, not on the total intensity of the band system, but on that part of it present in the particular vibronic transition. For somewhat greater splittings, interactions between different vibrational sub-levels become significant, leading to observed values between the limiting case just mentioned and those for large intermolecular interaction in which the band system behaves as if it were concentrated at a single frequency. This is the first of the new features of weaker systems; the second is that, first-order effects becoming rapidly very small, second-order disturbances caused by nearby strong systems become relatively important, leading to modified splittings and transfers of intensity between the weak and

TABLE 7. 2750 Å *System assigned* A_g–B_{2u} (*y polarised*).

n	First-order splitting	*a* Component (cm.$^{-1}$)	*b* Component (cm.$^{-1}$)	Splitting to the second order	Polarisation ratio, *a* : *b*
0	115	39	− 54	93	1 : 1·2
1	205	$h\nu$ + 75	$h\nu$ − 93	168	1 : 1·5
2	196	$2h\nu$ + 78	$2h\nu$ − 87	165	1 : 2·1
3	154	$3h\nu$ + 61	$3h\nu$ − 73	134	1 : 3·4
4	99	$4h\nu$ + 37	$4h\nu$ − 61	98	1 : 7·8
Conc. system	767	306	− 320	626	1 : 1·5

TABLE 8. 2750 Å *System assigned* A_g–B_{1u} (*z polarised*).

n	First-order splitting	*a* Component (cm.$^{-1}$)	*b* Component (cm.$^{-1}$)	Splitting to the second order	Polarisation ratio, *a* : *b*
0	9	− 57	− 60	3	1 : 3·1
1	14	$h\nu$ − 96	$h\nu$ − 102	6	1 : 2·8
2	11	$2h\nu$ − 87	$2h\nu$ − 95	8	1 : 2·4
3	8	$3h\nu$ − 67	$3h\nu$ − 81	14	1 : 2·0
4	5	$4h\nu$ − 45	$4h\nu$ − 67	12	1 : 1·2
Conc. system	48	− 336	− 352	16	1 : 2·8

the strong system. Now, however, in contrast to the first-order term, and because the vibrational spacing in one system is usually less than the separation of two electronic systems, the magnitude of the second-order term depends mainly on the total intensities in the electronic systems. Thus one sees that such effects will rapidly overtake first-order effects in weak systems, especially when there is a widely spread vibrational structure. Furthermore, the intensity ratios for different crystal axes are unaffected in the first order and so show a sharp dependence on the second-order terms. All of these features were recognised and discussed in connection with the spectrum of anthracene [4] and in the preliminary report on naphthalene [5] and need not be insisted upon here. They have also been discussed recently by Simpson and Peterson [13] in a more general context.

The intensity ratio *a* : *b* is 4·2 : 1 for a long-axis transition, and 1 : 7·3 for a short-axis transition, from the projections of molecular axes on crystal axes. The measured value [14] for the onset of the system is about 1 : 3. This value depends both on the polarisation properties of the transition at 2750 Å and on that at 2200 Å which under the influence of neighbour molecules imparts its own polarisation to the weaker system to some extent. One readily finds [5] that neither assignment for the *weak* system, coupled with a short-axis *intense* system, can lead to an intensity ratio near 1 : 3. The intense system must therefore be long-axis polarised as is its analogue in anthracene.[3] Accordingly, we list results in Tables 7 and 8 calculated for the members of the main progression ($h\nu$ = 1430 cm.$^{-1}$) in the 2750 Å naphthalene system separately for the two in-plane polarisation directions, but assuming in the derivation of both a long-axis intense system at 2200 Å.

[13] Simpson and Peterson, *J. Chem. Phys.*, 1957, **26**, 588.
[14] Craig and Lyons, *Nature*, 1952, **169**, 1102.

Values of the first-order splitting given in the second column for the several vibrational sub-levels may be compared with that for a concentrated system which has the same total intensity at a single frequency; their sum is equal to the concentrated-system value, but individually they are, of course, very much less, and the change in the second order (col. 5) is relatively a small one. Thus, in accordance with the earlier qualitative considerations, the concentrated-system approximation breaks down completely for weaker systems, particularly for the calculations of splitting; the average intensity ratio, on the other hand, differs much less from the concentrated-system value.

Experimental values of the splitting in the 2750 Å system are not known, but the measured polarisation ratio [14] of 1 : 3 indicates the assignment A_g–B_{1u} short-axis polarised, as for the corresponding anthracene system.

5. *The Dipole Sums.*—The quantitative results, as distinct from the qualitative features of intermolecular interactions in crystals, depend on the values of the dipole sums listed in Tables 3 and 6. Two important matters need to be mentioned in relation to them, one concerned with the method of evaluation and the other with the shape of the region over which the sum is taken. We postpone the second, and consider how the summation can be made for the special case of a sphere. Individual terms are given in expression (14), and the term may be found by term-by-term evaluation through a sphere of some chosen radius. If the radius of this sphere is big enough, the effect of a spherical shell of molecules external to it becomes that of a uniformly polarised shell which, according to classical electrostatics, contributes nothing to the field at the centre. In practice a radius of 20—30 Å gives an adequate convergence to the limiting value of the sum except in certain cases where a molecule which happens to make an exceptionally large contribution lies very close to the surface of the spherical region. The direct summation (DS) procedure is, of course, highly susceptible to such accidents of structure, and the Ewald–Kornfeld (EK) method for summation over an infinite sphere by a transformation leading to a rapidly convergent summation is in principle to be preferred. In practice the EK method is a little more laborious to apply than direct summation within a 20 Å sphere, but certainly less so than a 30 Å summation; moreover, the errors of the DS summation accumulate with the number of individual interactions included, so that no purpose is served in extending it to a large radius. The comparisons between the two methods in Tables 3 and 6 show a satisfying agreement which confirms the general correctness of the values given; for calculations of the crystal spectra we have used the EK values.

It was pointed out by Fox and Yatsiv [15] that the dipole–dipole summation for $\mathbf{k} = 0$ is identical with a problem familiar in electrostatics in relation to permanent rather than transition dipoles, namely, that the sum depends on the shape of the region over which interactions are considered, and therefore that some care must be taken in interpreting experimental results by comparing them with calculations of what is a special case, namely a sphere. However, in the one case (anthracene) in which results are available for an intense system the interpretation is unambiguous because the effects of change of shape on the calculated spectrum are too small to blur the distinction between long- and short-axis polarisations [5] and, this fact being noted, we can further see that in this case the experimental results are fitted better by calculations for a sphere than for any substantially different shape. These facts are evident in the results collected in Table 9 for the crystal spectrum related to the intense system of anthracene observed at 2500 Å in the vapour. To deal with the change of shape we proceed conventionally to consider the field acting on a molecule to be made up of three parts: first, the cavity field produced by the molecules contained in a large spherical cavity, then the fields associated respectively with the inner and outer surfaces of a uniformly polarised medium surrounding the cavity, the outer surface being that which defines the volume through which the summation is taken. The polarisation $\boldsymbol{P}$ of the medium is $\boldsymbol{M}/\Gamma$ where $\boldsymbol{M}$ is the transition dipole moment and Γ the volume of the unit cell of the crystal. The field of the inner (spherical) surface is $4\pi\boldsymbol{P}/3$,

[15] Fox and Yatsiv, *J. Chem. Phys.*, 1956, **24**, 1103.

that of the outer depends on its shape; for a sphere it is $-4\pi\boldsymbol{P}/3$, for a thin slab with $\boldsymbol{P}$ normal to the plane sides it is $-4\pi\boldsymbol{P}$, and with $\boldsymbol{P}$ parallel to the sides it is zero. For a transition dipole length of 1 Å and with use of the anthracene unit cell volume of 474·2 Å^3, we find that the energy of a dipole of length 1 Å in the polarising field is $-1026 \cos\theta$ in wave-number units, where θ is the angle between the dipole and field directions. This allows the results for cases A and C in Table 9 to be built from those for B. The experimental results are those of Craig and Hobbins,[3] and the calculations refer to shapes as follows: A and C are thin slabs with polarisation normal and parallel respectively to the plane sides, and B is a sphere. ΔE^{α} refers to the displacement of the *a*-polarised component

TABLE 9.

Shape	ΔE^{α} (cm.$^{-1}$)	ΔE^{β} (cm.$^{-1}$)	Splitting $\Delta E^{\alpha} - \Delta E^{\beta}$ (cm.$^{-1}$)	Shift $(\Delta E^{\alpha} + \Delta E^{\beta})/2$ (cm.$^{-1}$)
		Anthracene		
A	+33,300(−380)	−3900(+11,600)	+37,300(−12,000)	+14,700(+5600)
B	+12,000(−4700)	−4250(−5700)	+16,200(+1000)	+3850(−5200)
C	+1260(−6900)	−4400(−14,400)	+5700(+7500)	−1600(−10,700)
Exptl. (2500 Å system)	~+13,000	~−3000	~+16,000	~+5000
		Naphthalene		
A	+24,400(+2100)	−1900(+11,200)	+26,300(−9100)	+11,300(+6600)
B	+6600(−2400)	−2700(−3000)	+9300(+600)	+1900(−2700)
C	−2300(−4700)	−3200(−10,100)	+800(+5400)	−2800(−7400)

from the vapour value and the splitting is made positive when the *a* component is at higher frequencies than the *b*. The values in parentheses refer to short axis polarised molecular absorption. It is apparent that the observed value of the splitting is incompatible with a short-axis transition irrespective of assumption about shape, and, moreover, the sphere values fit better than either extreme departure from the spherical.

We are inclined to think that the difficulty over shape dependence will not arise when allowance is made for the fact that, at distances comparable to the length of the absorbed light wave, the intermolecular potential energy is not the static but the retarded potential.[16] It is certain that at such distances the interaction energy will not follow the static inverse-cube law and therefore that the analogy with the problem of permanent dipoles breaks down. The explanation may involve a cutting-off of the interaction at distances of the order of a wavelength, leading to a shape-independent sum. This is to be taken up in a later paper.

We thank Dr. E. A. Power and Dr. S. Zienau for several discussions.

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[*Received, November 5th*, 1957.]

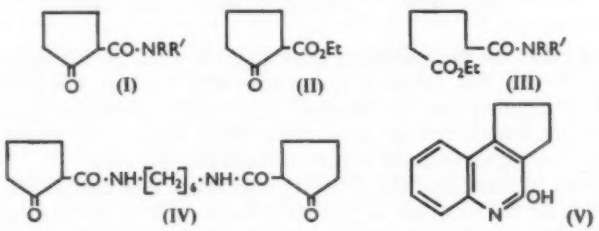
[16] Heitler, "The Quantum Theory of Radiation," 3rd edn., Oxford, 1954, p. 233.

323. *The Synthesis of* N-*Alkyl*-2-*oxo*cyclo*pentanecarboxyamides.*

By David H. Johnson.

N-Alkyl-2-oxo*cyclo*pentanecarboxyamides result from the action of metallic sodium on *N*-alkyladipamic esters in boiling benzene. Yields are low for the lower homologues of the series but rise to 60—70% for amides derived from amines having a chain-length of 4 carbon atoms or more. The method is not applicable to the synthesis of *NN*-dialkyl-2-oxo*cyclo*pentanecarboxyamides.

N-ALKYL-2-OXO*cyclo*PENTANECARBOXYAMIDES (I; R = H, R′ = Alkyl), which were required for studies of the thermal decomposition of Nylon 66 polymer during 1952—1956,[1] appear to have attracted no previous attention. Although several *N*-aryl analogues (I; R = H, R′ = Aryl), prepared by reaction of the ester (II) with amines, have been reported,[2] attempts by Mr. O. B. Edgar of these laboratories to extend these procedures to the aliphatic series were relatively unsuccessful. We have now found, however, that ethyl *N*-alkyladipamates (III; R = H, R′ = Alk) cyclise to the requisite β-keto-amides (I) under the base-catalysed conditions normally employed for the classical Dieckmann condensation,[3] *e.g.*, with sodium in boiling benzene, the experimental procedure being based



upon the optimum conditions for conversion of diethyl adipate into ethyl 2-oxo*cyclo*pentanecarboxylate (II). These conditions include the addition of a small amount of ethanol to eliminate or reduce any induction period,[4] and use of 1·4—1·5 atomic proportions of sodium.[5] The yields of amides (I) were lowest from amines of short chain-length and progressively increased to 60—70% for amines of chain-length equal to or greater than C_4 (see Table 2, p. 1626). The structure of a cyclisation product was demonstrated conclusively only for the butylamide, the structures of the homologues being inferred from their similar infrared absorption spectra and chemical properties.

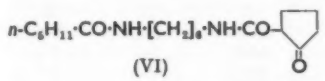
The butylamide afforded a crystalline 2 : 4-dinitrophenylhydrazone and semicarbazone and with ethanolic ferric chloride gave an intense royal blue colour similar to that given by the ester (II). Its infrared absorption was characterised by principal bands at 1742 cm.$^{-1}$ (*cyclo*pentanone ring), 3356, 3135, 1645, and 1507 cm.$^{-1}$ (CO·NH), and 2959, 2915, 1475, 1464, and 1385 cm.$^{-1}$ (CH_2 and Me). In hydrolytic behaviour the amide paralleled the ester: thus " ketonic " fission ensued in boiling 5N-hydrochloric acid, and " acidic " fission in boiling 20% aqueous sodium hydroxide.

The cyclisation procedure has been extended to the preparation, in 81% yield, of the

[1] Goodman, *J. Polymer Sci.*, 1954, **13**, 175; 1955, **17**, 587.
[2] (*a*) Blount, Perkin, and Plant, *J.*, 1929, 1975; (*b*) Linstead and Bao-Lang Wang, *J.*, 1937, 707; Ahmad and Desai, *Proc. Indian Acad. Sci.*, 1937, **5**, *A*, 543; Barany and Pianka, *J.*, 1947, 1420; Clemo and Mishra, *J.*, 1953, 192.
[3] Dieckmann, *Ber.*, 1894, **27**, 102, 965.
[4] Linstead and Meade, *J.*, 1934, 940.
[5] Pinkney, *Org. Synth.*, Coll. Vol. II, p. 116; Cornubert and Borrel, *Bull. Soc. chim. France*, 1930, **47**, 301.

di-β-ketoamide (IV) from the ester (III; R = H, R′ = $[CH_2]_6$·NH·CO·$[CH_2]_4$·CO_2Et) with 2·9 atomic proportions of sodium, and to the formation, in 67% yield from ethyl adipanilate (III; R = H, R′ = Ph), of 2-oxo-*N*-phenyl*cyclo*pentanecarboxyamide (I; R = H, R′ = Ph),[2] which, with concentrated sulphuric acid at 100°, gave 2-hydroxy-3 : 4-*cyclo*pentenoquinoline [2a, 6] (V). However, by the Dieckmann procedure ethyl *NN*-dialkyladipamates, such as (III; R = R′ = Pr^n or Bu^n), gave resins having none of the expected properties, whilst ethyl adipamate (III; R = R′ = H) under these conditions furnished only 9% of the ester (II) and no amide. Hence the reaction appears to be restricted to esters derived from primary amines. That cyclisation proceeds at all, however, is somewhat surprising in view of the greater electron-attracting propensities of ester groupings than of amides. This feature would be expected to lead to activation of the methylene group adjacent to the ethoxycarbonyl system rather than to that of the CH_2 in the α-position to the CO·NHR.[7] Activation of the appropriate methylene site may conceivably arise by a charge redistribution within an ionised transition state or by interchange of ester and amide groups within such a state.

The foregoing cyclisation has been used in a synthesis of an amide carrying an extended



(VI)

n-C_5H_{11}·CO·NH·$[CH_2]_6$·NH·R (VII)

R·NH·$[CH_2]_5$·CN (VIII)

N-substituent. Thus, the diamide (VI) has been obtained in 65% yield from the ester (VII; R = EtO_2C·$[CH_2]_4$·CO), which was prepared from 6-aminohexanonitrile (VIII; R = H) by way of (VIII; R = n-C_5H_{11}·CO) and (VII; R = H).

Experimental

Ethyl Adipamate (III; R = R′ = H).—Prepared by ammonolysis [8] of the acid chloride [9] (b. p. 114°/11 mm.) of ethyl hydrogen adipate [10] (b. p. 106—108°/0·1 mm., m. p. 28—29°), this ester formed colourless needles, m. p. 77°, from ethyl acetate–light petroleum (b. p. 80—100°) (Found: C, 55·3; H, 8·7; N, 8·0. Calc. for $C_8H_{15}O_3N$: C, 55·5; H, 8·7; N, 8·1%). Rauscher and Tucker [8] give m. p. 77—78°.

Ethyl N-*Alkyladipamates* (III; R = H, R′ = Alk).—The acid chloride (204 g., 1·06 moles) of ethyl hydrogen adipate in benzene (200 ml.) was added during 90 min. to a stirred mixture of the amine (1·07 moles), pyridine (93·5 g., 1·18 moles), and benzene (200 ml.) at 0—5°. Then the mixture was kept at 100° for 2 hr., benzene and excess of pyridine were removed in steam, and the product was extracted with chloroform (2 × 250 ml.; 3 × 75 ml.). After washings with 2N-hydrochloric acid (3 × 100 ml.), water (2 × 100 ml.), aqueous sodium hydrogen carbonate (2 × 100 ml.), and water (2 × 100 ml.), the combined chloroform solutions were dried ($MgSO_4$) and evaporated. Distillation of the residue afforded a small forerun and then the pure *ethyl* N-*alkyladipamate* (see Table 1).

N-*Alkyl*-2-*oxo*cyclo*pentanecarboxyamides* (I; R = H, R′ = Alkyl).—The ethyl *N*-alkyladipamate (0·874 mole) and ethanol (2 ml.) were added in one portion to an agitated suspension of powdered sodium (30 g., 1·305 g.-atom) in benzene (750 ml.), and the mixture gradually heated to boiling under reflux. Reaction quickly set in with, in the early stages, much frothing; the sodio-derivative began to separate after 2 hr. The mixture was boiled under reflux with stirring for 20 hr., then cooled and poured into 2N-hydrochloric acid (750 ml.), and the benzene layer separated. The aqueous residue was extracted further with benzene (5 × 75 ml.), and the combined benzene solutions were washed with aqueous sodium hydrogen carbonate

[6] (*a*) Beer, McGrath, and Robertson, *J.*, 1950, 3283; (*b*) Witkop, Patrick, and Rosenblum, *J. Amer. Chem. Soc.*, 1951, **73**, 2641.
[7] Cf. Hauser and Renfrow, *ibid.*, 1937, **59**, 1823; 1938, **60**, 463.
[8] Rauscher and Tucker, *J. Amer. Chem. Soc.*, 1954, **76**, 3599.
[9] Blaise and Koehler, *Bull. Soc. chim. France*, 1910, **7**, 219.
[10] Brown, Armstrong, Moyer, Anslow, Baker, Querry, Bernstein, and Safir, *J. Org. Chem.*, 1947, **12**, 163.

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(6 × 75 ml.) and water (2 × 75 ml.); these washings which contained some unidentified acid (*N*-alkyladipamic acid?) were discarded. The dried benzene solution was evaporated, and distillation of the residue then afforded the N-*alkyl*-2-*oxo*cyclo*pentanecarboxyamides* (see Table 2).

TABLE 1. *Ethyl* N-*alkyladipamates* (III).

No.	R	R′	Yield (%)	B. p./mm.	n_D^{20}	Forerun Yield * (%)	Forerun B. p./mm.
1	H	Me	61·6	132—134°/0·1	1·4575	15·5	60—120°/0·1
2	H	Et	79·3	124—126/0·1	1·4560	8·3	62—117/0·1
3	H	Pr^n	72·0	138—140/0·15	1·4549	4·2	80—136/0·15
4	H	Bu^n	81·5	134/0·09	1·4540	4·7	80—130/0·09
5	H	*n*-C_6H_{13}	75·5	158—160/0·15	1·4568	8·0	70—143/0·15
6	H	Ph	79·2	194—196/0·45	1·5273	4·7	94—198/0·5
7	Pr^n	Pr^n	66·9	119—120/0·1	1·4549	13·7	86—130/0·1
8	Bu^n	Bu^n	71·0	136—138/0·15	1·4569	14·5	82—140/0·15
9	H	$[CH_2]_6$·NH·CO·$[CH_2]_4$·CO_2Et	87·0	M. p. 111—112° (from EtOAc)	—	—	—

No.	Found (%) C	H	N	Formula	Required (%) C	H	N
1	57·3	9·2	7·7	$C_9H_{17}O_3N$	57·7	9·15	7·5
2	59·9	9·5	6·4	$C_{10}H_{19}O_3N$	59·7	9·5	7·0
3	61·5	9·7	6·3	$C_{11}H_{21}O_3N$	61·4	9·8	6·5
4	63·0	10·0	5·6	$C_{12}H_{23}O_3N$	62·85	10·1	6·1
5	64·9	10·0	4·9	$C_{14}H_{27}O_3N$	65·3	10·6	5·4
6	66·9	7·3	5·3	$C_{14}H_{19}O_3N$	67·4	7·7	5·6
7	65·0	10·3	5·2	$C_{14}H_{27}O_3N$	65·3	10·6	5·4
8	67·3	11·0	5·0	$C_{16}H_{31}O_3N$	67·3	10·95	4·9
9	61·5	9·4	6·0	$C_{22}H_{40}O_6N_2$	61·65	9·4	6·5

* Calc. as ethyl *N*-alkyladipamate.

TABLE 2. N-*Substituted* 2-*oxo*cyclo*pentanecarboxyamides* (I).

R	R′	Yield (%)	B.p./mm.	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
H	Me	9·5	80°/0·09	—	Unsatisfactory			$C_7H_{11}O_2N$	59·55	7·85	9·9
H	Et	38·0	—	84° [a]	62·0	8·1	9·1	$C_8H_{13}O_2N$	61·9	8·4	9·0
H	Pr^n	47·0	98/0·2	—	63·7	8·9	8·0	$C_9H_{15}O_2N$	63·9	8·9	8·3
H	Bu^n	65·0	103/0·05	—	65·5	9·5	7·7	$C_{10}H_{17}O_2N$	65·5	9·35	7·65
H	*n*-C_6H_{13}	62·0	130/0·1	—	68·4	9·8	6·4	$C_{12}H_{21}O_2N$	68·2	10·0	6·6
H	Ph	67·0	—	102—103 [b]	70·3	6·3	6·9	$C_{12}H_{13}O_2N$	70·9	6·5	6·9
H	*	81·0	—	98 [c]	63·9	8·6	7·7	$C_{18}H_{30}O_4N_2$	64·3	8·4	8·3

[a] From EtOAc. [b] From EtOAc–light petroleum (b. p. 80—100°) (lit.,[2,6] m. p. 104°). [c] From EtOAc–light petroleum (b. p. 60—80°).
* 6-(2-Oxo*cyclo*pentanecarboxyamido)hexyl [cf. (IV)].

TABLE 3. 2 : 4-*Dinitrophenylhydrazones of amides from Table* 2.

R	R′	Solvent ‡	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
H	Me	M	231—232° †	48·6	5·0	21·3	$C_{13}H_{15}O_8N_5$	48·6	4·7	21·8
H	Et	E	175—176	50·1	5·5	20·6	$C_{14}H_{17}O_8N_5$	50·1	5·1	20·9
H	Pr^n	E	177—178	51·2	5·3	20·3	$C_{15}H_{19}O_8N_5$	51·6	5·5	20·05
H	Bu^n	E	168	53·1	5·8	19·6	$C_{16}H_{21}O_8N_5$	52·9	5·8	19·3
H	*n*-C_6H_{13}	E	148	55·3	6·6	17·5	$C_{18}H_{25}O_8N_5$	55·2	6·4	17·9
H	Ph	E	190 [a]	56·7	4·6	18·4	$C_{18}H_{17}O_8N_5$	56·4	4·5	18·3
H	*	M	214 †	51·7	5·5	20·4	$C_{30}H_{36}O_{16}N_{20}$	51·7	5·2	20·1

* As footnote of Table 2. † With decomp. ‡ E = ethanol; M = 2-methoxyethanol.
[a] Beer *et al.*[6a] give m. p. 182°.

The 2 : 4-*dinitrophenylhydrazones* (see Table 3) were prepared in boiling ethanol containing hydrochloric acid, and the *semicarbazone* derivatives (see Table 4) by the sodium acetate method. Apart from 2-oxo-*N*-phenyl*cyclo*pentanecarboxyamide (I; R = H, R′ = Ph) which gave an intense green-blue colour, all the keto-amides had intense royal-blue ferric reactions in ethanol.

2-Hydroxy-3 : 4-cyclopentenoquinoline (V).—A solution of *N*-phenyl-2-oxo*cyclo*pentanecarboxyamide (1 g.) in concentrated sulphuric acid (7·5 ml.) was kept at 100° for 15 min., then poured into water (400 ml.). Purification of the resulting precipitate, from aqueous acetic acid, gave 2-hydroxy-3 : 4-*cyclo*pentenoquinoline in pale yellow needles, m. p. 259° (Found: C, 77·9; H, 6·1; N, 7·0. Calc. for $C_{12}H_{11}ON$: C, 77·8; H, 6·0; N, 7·6%), which gave a pale orange ferric reaction in alcohol and had an infrared absorption spectrum identical with that recorded by Witkop *et al.*[6] (lit., m. p. 256°,[2a, 6b] 262° [6a]).

TABLE 4. *Semicarbazones of amides from Table 2.*

				Found (%)				Required (%)		
R	R′	Solvent *	M. p.	C	H	N	Formula	C	H	N
H	Me	M	219—220°	48·6	6·9	28·1	$C_8H_{14}O_2N_4$	48·5	7·1	28·3
H	Et	M	207—208	51·3	7·5	26·6	$C_9H_{16}O_2N_4$	50·9	7·6	26·4
H	Pr^n	M	210	53·2	8·5	—	$C_{10}H_{18}O_2N_4$	53·1	8·0	24·8
H	Bu^n	M	208 (decomp.)	55·0	8·3	23·1	$C_{11}H_{20}O_2N_4$	55·0	8·4	23·3
H	*n*-C_6H_{13}	M	209	58·2	8·9	20·7	$C_{13}H_{24}O_2N_4$	58·2	9·0	20·9
H	Ph	E	220—221 †	60·6	6·1	21·5	$C_{13}H_{16}O_2N_4$	60·0	6·2	21·5

* As in Table 3. † With decomp. (slow heating); 227° (decomp.) (rapid heating).

Attempted Cyclisation of Ethyl Adipamate (III; R = R′ = H).—Ethyl adipamate (III; R = R′ = H) (7·0 g.) with sodium (1·35 g.) in benzene (100 ml.) gave ethyl 2-oxo*cyclo*pentanecarboxylate (0·58 g.), b. p. 116—118°/32 mm., n_D^{20} 1·4571 (blue ferric reaction in alcohol; infrared absorption) (Found: C, 60·9; H, 8·0. Calc. for $C_8H_{12}O_3$: C, 61·5; H, 7·75%). The 2 : 4-dinitrophenylhydrazone separated from ethanol in yellow needles, m. p. and mixed m. p. 128° (Found: C, 50·3; H, 4·9; N, 16·7. Calc. for $C_{14}H_{16}O_6N_4$: C, 50·0; H, 4·8; N, 16·7%).

Hydrolysis of N-*Butyl-2-oxo*cyclo*pentanonecarboxyamide.*—(a) *With* 5N-*hydrochloric acid.* The amide (5·7146 g., 1 mol.) was boiled under reflux for 3 hr. with 5N-hydrochloric acid (100 ml.) whilst nitrogen was led through the mixture; carbon dioxide (1·3662 g., 0·995 mol.) in the dried gases was absorbed on "Carbosorb" soda-lime asbestos. The aqueous residue was steam-distilled until a drop of the distillate no longer gave a precipitate with acidic 2 : 4-dinitrophenylhydrazine solution. The total steam-distillate was then diluted to 500 ml. and a 100 ml. portion was boiled under reflux for 1 hr. with 2 : 4-dinitrophenylhydrazine (1·35 g.) in concentrated sulphuric acid (35 ml.) and water (270 ml.). The cooled mixture was kept at 20° overnight and, next day, the yellow precipitate (1·4528 g., 0·88 mol.) was collected, washed, dried, and recrystallised from methanol to yield *cyclo*pentanone 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 144° (Found: C, 50·1; H, 4·4; N, 21·5. Calc. for $C_{11}H_{12}O_4N_4$: C, 50·0; H, 4·6; N, 21·2%).

The acidic residue from the steam-distillation was basified with 20% sodium hydroxide solution and boiled under reflux in a current of nitrogen. The gases were led through N-hydrochloric acid (50·00 ml.) and found by back-titration to contain *n*-butylamine (0·946 mol.), which was isolated as the 2 : 4-dinitrophenyl derivative, yellow needles (from methanol), m. p. and mixed m. p. 92°.

(b) *With* 20% *aqueous sodium hydroxide.* The amide (6·2767 g., 1 mol.) was boiled under reflux for 5 hr. with 20% aqueous sodium hydroxide (100 ml.) in a current of nitrogen. The gases were led into N-hydrochloric acid (50·00 ml.) and found by back-titration to contain *n*-butylamine (0·921 mol.), isolated as N-*n*-butyl-2 : 4-dinitroaniline, m. p. and mixed m. p. 92°.

No significant quantity of carbon dioxide (as measured by absorption on "Carbosorb" soda-lime asbestos) was liberated when the residual alkaline hydrolysate was acidified and boiled under reflux for 2 hr., but, from the cooled mixture, adipic acid (4·00 g., 0·799 mol.) was isolated by continuous ether-extraction and purified from water in needles, m. p. and mixed m. p. 151—152°.

N-(*5-Cyanopentyl*)*hexanamide* (VIII; R = *n*-C_5H_{11}·CO).—Hexanoyl chloride (37 g.) in benzene (35 ml.) was added dropwise to a stirred mixture of 6-aminohexanonitrile (30·8 g.), pyridine (21·7 g.), and benzene (120 ml.) at 0—5°. The mixture was stirred overnight at room temperature and next day was heated at 100° for 1 hr. Benzene and excess of pyridine were removed in steam, and the residue was extracted with chloroform (6 × 50 ml.). After successive washings with 2N-hydrochloric acid (6 × 75 ml.), aqueous sodium hydrogen carbonate

(6 × 50 ml.), and water (3 × 50 ml.), the extract was dried and the solvent evaporated. Distillation of the residue afforded N-(5-*cyanopentyl*)*hexanamide* (49 g.), b. p. 168°/0·1 mm. (Found: C, 69·2; H, 10·8; N, 13·1. $C_{18}H_{22}ON_2$ requires C, 68·5; H, 10·5; N, 13·3%).

N-(6-*Aminohexyl*)*hexanamide* (VII; R = H).—Hydrogen (15·4 l., 2·8 mol.) was absorbed when *N*-(5-cyanopentyl)hexanamide (49 g.) in dioxan (200 ml.) was hydrogenated at 100°/150 atm. over cobalt–kieselguhr (10 g.) in the presence of anhydrous ammonia (35 ml.). After catalyst had been removed, the solution was acidified with 2N-hydrochloric acid and evaporated to dryness. An aqueous solution (200 ml.) of the residue was washed with chloroform (3 × 75 ml.), then basified with 10% aqueous sodium hydroxide and extracted with chloroform (7 × 75 ml.). Distillation of the residue left on evaporation of the dried extract afforded *N*-(6-aminohexyl)hexanamide (43 g.), b. p. 148°/0·1 mm.; this compound rapidly carbonated and analysis was unsatisfactory.

Acylation with hexanoyl chloride and pyridine at 100° furnished 1 : 6-dihexanamidohexane, which crystallised from ethyl acetate in needles, m. p. and mixed m. p. 142—143° (Goodman,[11] 141—142°) (Found: C, 68·7; H, 11·6; N, 8·6. Calc. for $C_{18}H_{36}O_2N_2$: C, 69·2; H, 11·6; N, 9·0%).

Ethyl N-(6-*Hexanamidohexyl*)*adipamate* {VII; R = $EtO_2C{\cdot}[CH_2]_4{\cdot}CO$}.—Prepared by the dropwise addition of the acid chloride of ethyl hydrogen adipate (87 g.) in benzene (150 ml.) to an agitated ice-cold mixture of *N*-(6-aminohexyl)hexanamide (87 g.), pyridine (45 ml.), and benzene (250 ml.), this *diamide* (136 g.), isolated in the usual way with chloroform, was purified from ethanol and then ethyl acetate, and obtained as needles, m. p. 115—116° (Found: C, 64·4; H, 10·3; N, 7·8. $C_{22}H_{38}O_4N_4$ requires C, 64·8; H, 10·3; N, 7·6%).

N-(6-*Hexanamidohexyl*)-2-*oxo*cyclo*pentanecarboxyamide* (VI).—A stirred mixture of the preceding ester-amide (75 g.), absolute ethanol (1 ml.), benzene (400 ml.), and sodium (6·8 g.) was boiled under reflux for 16 hours. The *product*, isolated in the normal manner, crystallised from ethyl acetate in needles (42—47 g., 64—71·5%), m. p. 108—109°, which had an intense royal-blue ferric reaction in ethanol (Found: C, 66·3; H, 10·0; N, 9·1. $C_{18}H_{32}O_3N_2$ requires C, 66·6; H, 9·9; N, 8·6%). The infrared spectrum (Nujol mull) had principal absorption bands at 3378ms, 3115m, 2941—2890s, 1742ms, 1639s, 1541s, 1468s, 1385ms, 1261m, 1236m, 1217m, 1143m, 1064w, 980w, 952w, 838w, and 728m cm.$^{-1}$.

The amide (VI) formed a 2 : 4-*dinitrophenylhydrazone* as orange needles (from aqueous methanol), m. p. 170—171° (Found: C, 57·0; H, 7·3; N, 16·7. $C_{24}H_{36}O_6N_4$ requires C, 57·1; H, 7·2; N, 16·7%), and a *semicarbazone*, colourless needles (from aqueous methanol), m. p. 205—206° (Found: C, 60·0; H, 9·3; N, 18·8. $C_{19}H_{35}O_3N_5$ requires C, 59·8; H, 9·2; N, 18·4%).

Acid hydrolysis, essentially as above, gave carbon dioxide (0·89 mol.), volatile acid (0·934 equiv.), and *cyclo*pentanone 2 : 4-dinitrophenylhydrazone (1·06 mol.), m. p. and mixed m. p. 144°. A volatile acid was isolated and shown by paper chromatography to be hexanoic acid containing a trace of acetic acid. 1 : 6-Diaminohexane was also isolated and was shaken for 24 hr. with ethanol (30 ml.), anhydrous potassium carbonate (7·5 g.), and 1-fluoro-2 : 4-dinitrobenzene (2·3 g.); the mixture was then filtered, washed with water, and dried. The yellow solid (3·026 g., 1·09 mol.) separated from nitrobenzene in yellow needles, m. p. 205° alone or admixed with the authentic bis-2 : 4-dinitrophenyl derivative (lit.,[12] m. p. 205°).

The author thanks Mr. M. StC. Flett for the measurement of the infrared spectra, Mr. R. Rothwell and his staff for the microanalyses, and Mr. D. A. Alker for technical assistance.

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[*Received, November 15th*, 1957.]

[11] Goodman, personal communication.
[12] Zahn, Kocklauner, Rathgeber, and Gerstner, *Makromol. Chem.*, 1954, **12**, 35.

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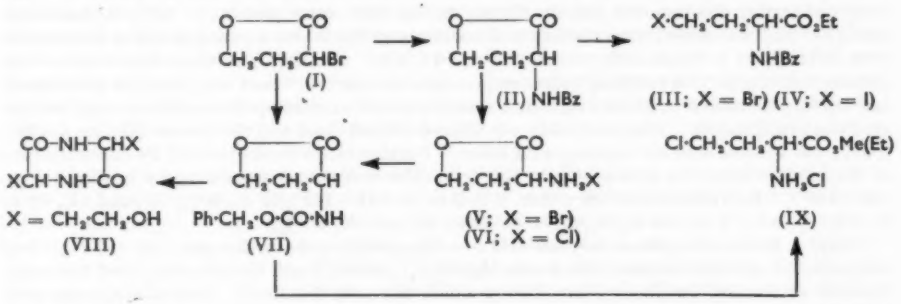
324. *Improved Preparation of Intermediates for the Syntheses of α-Aminobutyric Acid Derivatives having Functional γ-Substituents.*

By Y. Knobler and Max Frankel.

New syntheses have been worked out for γ-halogenated derivatives of α-aminobutyric acid, intermediates for the preparation of α-amino-acids having functional γ-substituents.

The use of trifunctional key substances bearing an exchangeable atom in the γ-positions represents the principal step in the syntheses of methionine [1,2,3] cystathionine,[4] homolanthionine,[4] canaline,[5,6] and selenium analogues of methionine and homocystine.[7] In principle, two general steps can be distinguished in synthesising such derivatives of α-aminobutyric acids by this method: the first consists in building up the trifunctional intermediate containing both the amino- and the carboxyl group either protected or inactivated by inner bonding; the second involves the introduction of the characteristic group at the γ-position. A final step is liberation from the protecting groups or cleavage of intramolecular bonds.

In our investigations it was of practical interest to render some γ-halogenated derivatives of homoserine (α-amino-γ-hydroxybutyric acid) more available; α-bromo-γ-butyrolactone (I), described by Livak *et al.*,[3] seemed to be the most suitable starting material.



From this, α-benzamido-γ-butyrolactone (II) was prepared by treatment with ammonia, alkaline hydrolysis of the resulting α-amino-γ-hydroxybutyramide, benzoylation of the sodium salt of homoserine, acidification, and heating with dilute hydrochloric acid (overall yield 60%). All these steps were carried out without isolation of intermediates.

Prolonged treatment of α-benzamido-γ-butyrolactone (II) in absolute ethanol with dry hydrogen bromide or iodide, at moderate temperatures, gave ethyl α-benzamido-γ-bromo-(or iodo)butyrate (III, 80%; IV, 75% yield). Both were used in the synthesis of DL-canaline.[6]

α-Benzamido-γ-butyrolactone (II) was debenzoylated by hydrochloric or hydrobromic acid, whereby the salts (V, VI) of α-amino-γ-butyrolactone were obtained almost quantitatively. The hydrobromide (V) represented the last intermediate in the synthesis of homoserine by E. Fischer and Blumenthal [8] and from it the dioxopiperazine (VIII) has been obtained.[3]

A different approach, also based on α-bromo-γ-butyrolactone (I), involved protection

[1] Hill and Robson, *Biochem. J.*, 1936, **30**, 248.
[2] Snyder, Andreen, Cannon, and Peters, *J. Amer. Chem. Soc.*, 1942, **64**, 2082.
[3] Livak, Britton, VanderWeele, and Murray, *ibid.*, 1945, **67**, 2218.
[4] Stekol, *J. Biol. Chem.*, 1948, **173**, 153.
[5] Kitagawa, *J. Agric. Chem. Soc. Japan*, 1936, **12**, 871.
[6] Knobler and Frankel, following paper.
[7] Painter, *J. Amer. Chem. Soc.*, 1947, **69**, 232.
[8] Fischer and Blumenthal, *Ber.*, 1907, **40**, 106.

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of the amino-group of the homoserine by the benzyloxycarbonyl group. By a series of steps analogous to the preparation of α-benzamido-γ-butyrolactone (II), α-benzyloxycarbonylamino-γ-butyrolactone (VII) was obtained in 30% overall yield. α-Amino-γ-butyrolactone hydrobromide (V) gave α-benzyloxycarbonylamino-γ-butyrolactone (VII) in 63% yield (36% based on I). Removal of the protecting group by hydrogenolysis gave the free aminobutyrolactone which was dimerised to the dioxopiperazine [8] (VIII). This compound may be converted into 2 : 5-di-(2-chloroethyl)-3 : 6-dioxopiperazine, a dimeric intermediate for the preparation of α-aminobutyric acids having functional γ-substituents.[2,4] Treating the lactone (VII) with dry hydrochloric acid in absolute methanol or ethanol afforded the ester hydrochlorides (IX) of α-amino-γ-chlorobutyric acid.

Experimental

M. p.s were determined in a Fisher–Johns apparatus.

α-Benzamido-γ-butyrolactone (II).—α-Bromo-γ-butyrolactone (I) (82·5 g.) was dissolved with gentle shaking in 25% aqueous ammonia (350 ml.) at 0° and the solution was kept closed at room temperature for 6 days. N-Sodium hydroxide (1500 ml.) was added and the excess of ammonia was removed by stirring the solution in a boiling-water bath. After 2 hr. the mixture was cooled to 0°, stirred rapidly, and benzoyl chloride (210 g.) and 4N-sodium hydroxide (1 l.) were slowly added simultaneously, at such a rate that the solution remained alkaline (*ca.* 3 hr.). Stirring was then continued for 1 hr. at 0° and for 2 more hours at room temperature. Undissolved matter was removed and the filtrate diluted with water (500 ml.). 18% Hydrochloric acid (700 ml.) was added with stirring and cooling and the white foaming mixture was heated with stirring on a water-bath at 80—90° for 45 min. Heating was then discontinued but stirring continued. On reaching room temperature the reaction vessel was placed in an ice-bath and stirring continued until the crystalline mixture of α-benzamido-γ-butyrolactone and benzoic acid was precipitated. The precipitate was filtered off and dried and the lactone (II), m. p. 138°, freed from benzoic acid by washing with ether. Further crops were obtained by concentration of the mother-liquor on a steam-bath, the crystalline compound separating on cooling (m. p. 139—140°). Recrystallised from water, it had m. p. 141—142° (62 g., 60%) (Found: C, 64·1; H, 5·6; N, 6·8. Calc. for $C_{11}H_{11}O_3N$: C, 64·4; H, 5·4; N, 6·8%).

Ethyl α-Benzamido-γ-bromobutyrate (III).—α-Benzamido-γ-butyrolactone (II) (10·2 g.) was suspended in absolute ethanol [dried over $Mg(OEt)_2$] (300 ml.) and treated with dried hydrogen bromide at 40—45° for about 3 hr., during which the solid dissolved. The solution was then kept at room temperature with exclusion of moisture for 24 hr. and concentrated *in vacuo*. Some resin was filtered off from the cooled solution and the filtrate again concentrated until syrupy. It was then twice diluted by small portions of ethanol, concentrated *in vacuo*, and finally dissolved in ethanol (150 ml.). The solution was cooled to 0° and small portions of water were added with shaking and cooling until it became cloudy. The mixture was left at 0°, the *ester* separating in white fine crystals (if coloured they were purified by washing with very dilute sulphurous acid). The crystals were collected and further amounts obtained from the mother-liquor by precipitation with water as before (m. p. 75—80°). Recrystallisation from ethanol raised the m. p. to 83—84° (yield 12·6 g., 80%) (Found: C, 49·4; H, 5·1; N, 4·6; Br, 25·4; OEt, 14·4. $C_{13}H_{16}O_3NBr$ requires C, 49·7; H, 5·1; N, 4·5; Br, 25·5; OEt, 14·3%).

Ethyl α-Benzamido-γ-iodobutyrate (IV).—α-Benzamido-γ-butyrolactone (II) (10·2 g.) was treated with hydrogen iodide dried by glass wool sprayed with phosphoric oxide. A controlled rate of passage of gas and a precaution against sucking back were achieved by working under carbon dioxide atmosphere. Precipitated from ethanol with water and washed with cold 0·5% sulphurous acid, the *γ-iodobutyrate* (IV) (13·5 g., 75%) melted at 88—92°. Recrystallised from ethanol it melted at 94—95° (Found: C, 43·6; H, 4·3; N, 3·9; I, 35·0; OEt, 13·0. $C_{13}H_{16}O_3NI$ requires C, 43·2; H, 4·4; N, 3·9; I, 35·2; OEt, 12·5%).

α-Amino-γ-butyrolactone Hydrobromide (V).—α-Benzamido-γ-butyrolactone (10·25 g.) was refluxed in 15% hydrobromic acid (120 ml.) for 2 hr. From the cooled mixture, benzoic acid was removed by filtration and subsequent extraction with ether. The solution was evaporated *in vacuo* to dryness and the residue washed with small portions of absolute ethanol and ether. The hydrobromide (V) (8·5 g., 93%) had m. p. 225° (decomp.) (Found: C, 26·2; H, 4·6; N, 7·7; Br, 44·3. Calc. for $C_4H_8O_2NBr$: C, 26·4; H, 4·4; N, 7·7; Br, 43·9%).

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α-Amino-γ-butyrolactone Hydrochloride (VI).—Hydrolysis of the lactone (5·1 g.) in 15% hydrochloric acid (100 ml.) gave the hydrochloride (3·3 g., 96%), m. p. 203° (decomp.) (Found: N, 9·9; Cl, 26·0. Calc. for $C_4H_8O_2NCl$: N, 10·2; Cl, 25·8%).

α-Benzyloxycarbonylamino-γ-butyrolactone (VII).—(a) *From α-bromo-γ-butyrolactone* (I). α-Bromo-γ-butyrolactone (20·6 g.) was kept in 25% aqueous ammonia (100 ml.) for 4—5 days. N-Sodium hydroxide (375 ml.) was added and the mixture heated with stirring on a boiling-water bath for 2 hr. Water (100 ml.) was added and the solution cooled to 0°. 4N-Sodium hydroxide (35 ml.) and benzyl chloroformate (25 g.) were added simultaneously in portions during 2 hr. Stirring was continued for ½ hr. with cooling and for 2 more hours at room temperature. The mixture was extracted with ether and acidified with 18% hydrochloric acid. A crude viscous layer separated which was recrystallised from hot water. The *lactone* (VII) (9 g., 30%) had m. p. 105—108° (Found: C, 61·4; H, 5·6; N, 5·8. $C_{13}H_{13}O_4N$ requires C, 61·3; H, 5·5; N, 6·0%).

(b) *From the α-amino-γ-butyrolactone hydrobromide* (V). The hydrobromide (36·4 g.) was dissolved in water (750 ml.) and cooled to 0° and pyridine (80 ml.) added with stirring. Benzyl chloroformate (39 g.) was introduced in 2 hr. and stirring was continued for 1 hr. more with cooling and 2 hr. without cooling. The product separated. It was washed with light petroleum and dried (P_2O_5) (m. p. 108—110°). Recrystallisation from ether–light petroleum raised the m. p. to 110—112° (yield 29·6 g., 63%) (Found: C, 61·3; H, 5·5; N, 5·9%).

2 : 5-*Di*-(2-*hydroxyethyl*)-3 : 6-*dioxopiperazine* (VIII).—α-Benzyloxycarbonylamino-γ-butyrolactone (VII) (4·7 g.) was suspended in absolute alcohol (100 ml.), palladium chloride on carbon (1 g.; 1 : 3) was added, and the mixture hydrogenated at 30—35°/2 atm. for 7—8 hr. The catalyst was removed, the solution concentrated until cloudy, and α-amino-γ-butyrolactone hydrochloride filtered off. Absolute ethanol (150 ml.) was added and the solution refluxed for 24 hr. It was then decolorised with Norite, filtered, concentrated *in vacuo*, and cooled, and the product collected (m. p. 186°; 0·45 g., 22%). The mother-liquor was evaporated *in vacuo*, and the viscous residue dissolved in a small amount of hot ethanol, reprecipitated by ether, and washed with small portions of cold ethanol–ether (1 : 1). This material (0·45 g., 22%) had m. p. 184° (Found: N, 13·9. Calc. for $C_8H_{14}O_4N_2$: N, 13·9%).

Methyl α-Amino-γ-chlorobutyrate Hydrochloride (IX).—α-Benzyloxycarbonylamino-γ-butyrolactone (4·7 g.) was suspended in dry methanol (150 ml.) at 50—55° and a stream of dry hydrogen chloride was passed in for 4—5 hr. during which a clear solution resulted. The methanol was removed *in vacuo*, dry ethanol was added, and the solution cooled and freed from α-amino-γ-butyrolactone hydrochloride by filtration. By addition of dry ether a mixture of the hydrochlorides of the lactone (VI) and of the ester (IX) was precipitated. Portions of cold absolute ethanol were added, the undissolved amino-lactone hydrochloride filtered off, and *methyl α-amino-γ-chlorobutyrate hydrochloride* (IX) (1·2 g., 32%), m. p. 120°, reprecipitated (Found: N, 7·2; Cl, 38·0; OMe, 16·5. $C_5H_{11}O_2NCl_2$ requires N, 7·4; Cl, 37·8; OMe, 16·5%).

By a similar procedure, on passing hydrogen chloride through an ethanolic solution of α-benzyloxycarbonylamino-γ-butyrolactone (VII), the corresponding partly crystalline *ethyl ester hydrochloride* was obtained but in poorer yield (Found: N, 6·8; Cl, 35·4; OEt, 22·5. $C_6H_{13}O_3NCl_2$ requires N, 6·9; Cl, 35·1; OEt, 22·3%). After hydrogen chloride had passed through a suspension of the lactone (VII) in ethanol without heating, the lactone was recovered. When the same reaction was carried out under reflux only α-amino-γ-butyrolactone hydrochloride was obtained.

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325. *Synthesis of* DL-*Canaline and Some of its Derivatives.*

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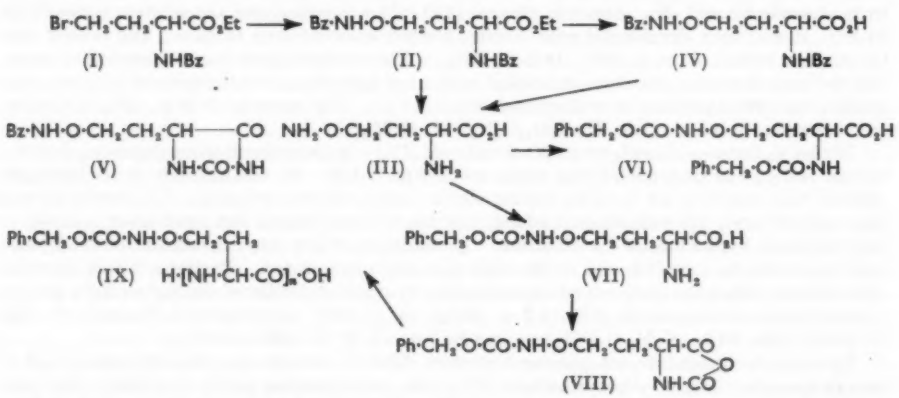
DL-Canaline was prepared in a 5-step synthesis from γ-butyrolactone in 21% overall yield. Conditions for introduction of the amino-oxy-group by means of benzhydroxamic acid and for the liberation of DL-canaline from its picrate and salts were worked out.

α-Benzyloxycarbonylamino-γ-benzyloxycarbonylamino-oxy- and γ-benzyloxycarbonylamino-oxy-derivatives of DL-canaline were prepared. The latter served for the preparation of its α-*N*-carboxy-anhydride which polymerised to a benzyloxylcarbonyl derivative of poly-DL-canaline.

DURING the last few years we have been working out convenient syntheses of canaline,[1] (α-amino-γ-amino-oxybutyric acid), canavanine (the γ-guanidinoxy-derivative), and related substances.

Canaline is produced by enzymic cleavage of canavanine which was detected in jack bean by Kitagawa and his co-workers who also succeeded in clarifying the structure of these two amino-acids.[2] By hydrogenation of the natural L-canaline, α-amino-γ-hydroxybutyric acid was obtained, from an appropriate derivative of which, on introduction of the amino-oxy-group, the L-canaline was finally regenerated. Although this procedure does not imply a practicable synthesis of canaline, the constitution was thus proved.



We report below a synthesis of DL-canaline based on ethyl DL-α-benzamido-γ-bromobutyrate [3] (I). This was condensed with benzhydroxamic acid in absolute ethanol in the presence of sodium ethoxide. The resulting ethyl DL-α-benzamido-γ-benzamido-oxybutyrate (II) (55%) was hydrolysed by dilute hydrochloric acid and DL-canaline (III) was obtained by treatment of the resulting DL-canaline dihydrochloride with triethylamine in aqueous ethanol in 85% yield (21% overall, based on γ-butyrolactone). The introduction of the amino-oxy-group by means of benzhydroxamic acid was also effected under milder conditions, in aqueous-alcoholic alkali or by ethanolic triethylamine.

A derivative with differently masked α-amino- and γ-amino-oxy-groups, the hydantoin (V), was obtained on condensation of benzhydroxamic acid with 5-2′-bromoethylhydantoin.[4]

[1] This work was completed before the publication of a synthesis in 7% overall yield of DL-canaline by Nyberg and Christensen (*J. Amer. Chem. Soc.*, 1957, **79**, 1222); cf. Y. Knobler, Ph.D. Thesis, Jerusalem, 1957; *Bull. Res. Council Israel*, 1957, **6**, 296.

[2] See Kitagawa, *J. Biochem.* (*Japan*), 1937, **25**, 23.

[3] Knobler and Frankel, preceding paper.

[4] Livak, Britton, VanderWeele, and Murray, *J. Amer. Chem. Soc.*, 1945, **67**, 2218.

Alternatively the ester (II) was hydrolysed in aqueous potassium hydroxide to the acid (IV) which was debenzoylated by aqueous sulphuric acid, the acid being then removed as barium salt. However, the DL-canaline thus obtained contained impurities from which it could not be freed conveniently.

We desired to polymerise DL-canaline by the Leuchs anhydride method; first we tried unsuccessfully to obtain the *N*-carboxy-anhydride (VIII) by the action of thionyl chloride on the di(benzyloxycarbonyl) derivative (VI) of DL-canaline. The *N*-carboxy-anhydride (VIII) was however obtained on treatment, with carbonyl chloride, of the derivative (VII) which resulted preferentially from the condensation of DL-canaline with 1 mol. of benzyl chloroformate. Heating the anhydride *in vacuo* yielded the benzyloxycarbonyl derivative (IX) of poly-DL-canaline.

Experimental

M. p.s were determined in a Fisher–Johns apparatus. The ascending method of paper-chromatography was used (80% phenol).

Ethyl DL-α-*Benzamido-γ-benzamido-oxybutyrate* (II).—(a) *By condensation of benzhydroxamic acid with ethyl* DL-α-*benzamido-γ-bromobutyrate* (I). To a solution of sodium ethoxide made from sodium (1·65 g.) and absolute ethanol [dried over $Mg(OEt)_2$] (70 ml.) was added a solution of benzhydroxamic acid (9·9 g.) in absolute ethanol (70 ml.). To the well-stirred suspension of the benzhydroxamic salt thus obtained was added a solution of ethyl α-benzamido-γ-bromobutyrate (I) (12·56 g.) in absolute ethanol (70 ml.). The stirred mixture was kept at 55—65° for 10—12 hr. The solution was cooled, filtered, and cooled at 0°. Water was added gradually to incipient cloudiness, and the mixture kept at 0° for crystallisation, and filtered; and addition of water, etc., was repeated. The crystals were dried (P_2O_5), washed with dry ether, and again dried (P_2O_5 *in vacuo*). The pure *ester* (8·15—8·9 g., 55—60%) had m. p. 122—124° (if ethyl α-benzamido-γ-iodobutyrate [2] was used the yield was only 40—45%) (Found: C, 64·7; H, 6·0; N, 7·6; OEt, 12·2. $C_{20}H_{22}O_5N_2$ requires C, 64·9; H, 6·0; N, 7·6; OEt, 12·2%).

(b) *By condensation of benzhydroxamic acid with ethyl α-benzamido-γ-iodobutyrate.* (i) Ethyl DL-α-benzamido-γ-iodobutyrate [2] (36·1 g.) in ethanol (200 ml.) was added to a mixture of benzhydroxamic acid (20·56 g.) in ethanol (400 ml.) with potassium hydroxide (8·4 g.) in water (50 ml.). Water (350 ml.) was added, most of the precipitated potassium benzhydroxamate dissolving. The mixture was heated with stirring at 40—45° for 18—20 hr., then cooled, and filtered, and the bulk of the ethanol was removed under reduced pressure. An oil separated which partly crystallised. The mixture was cooled to complete precipitation. Water was removed by decantation and the crude product washed with water, warmed at 40—50°, then cooled at 0°. Generally a crude white solid was obtained which, after drying (P_2O_5) and washing with dry ether, was pure enough for further reaction. If a crude soft product was obtained, purification could not be effected solely by washing with dry ether: reprecipitation from aqueous ethanol solution was necessary. Soft material obtained was dissolved in ethanol and precipitated as described under (a). The pure substance (15 g., 40%), had m. p. 122—124° (if ethyl DL-α-benzamido-γ-bromobutyrate was used, the yield was much poorer) (Found: C, 64·6; H, 6·1; N, 7·5; OEt, 12·2%).

(ii) To benzhydroxamic acid (8·9 g.) in absolute ethanol (150 ml.) was added triethylamine (6·5 g.) followed by ethyl DL-α-benzamido-γ-iodobutyrate (18·5 g.) in ethanol (75 ml.). The mixture was warmed at 50—55° and stirred for 15—16 hr., then cooled and filtered, and the filtrate was worked up as described under (a), but the time required for crystallisation was much longer. The ester (II) (8·3 g., 45%) melted at 123—124° (Found: C, 64·7; H, 6·0; N, 7·6; OEt, 12·2%).

DL-α-*Benzamido-γ-benzamido-oxybutyric Acid* (IV).—Ethyl DL-α-benzamido-γ-benzamido-oxybutyrate (II) (11·1 g.) was refluxed for 2 hr. with 0·5% aqueous sodium hydroxide (250 ml.). The solution was cooled, filtered, and acidified with 10% hydrochloric acid to Congo-red. The mixture, from which an oil separated, was warmed, shaken, allowed to cool, and chilled at 0° until the oil became semisolid. The supernatant layer was removed by decantation and the precipitate washed with water. The mother-liquor and washings were concentrated *in vacuo* and a further crop of substance was recovered. The combined crude products were dissolved in alcohol, and a little ether was added, followed by an excess of light petroleum. On cooling, the *acid* (IV) separated, having m. p. 158—160° (9·2—9·8 g., 90—95%) (Found: C, 63·1; H,

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5·3; N, 8·1. $C_{18}H_{18}O_5N_2$ requires C, 63·1; H, 5·3; N, 8·2%); it gave negative ninhydrin and Jaffe's tests and hydrolysis with 10% hydrochloric acid liberated DL-canaline and two equivalents of benzoic acid.

DL-*Canaline* (DL-α-*Amino-γ-amino-oxybutyric Acid*) (III).—(a) The γ-benzamido-oxy-ester (II) (11·1 g.) was refluxed with 12% hydrochloric acid (400 ml.) during 4 hr., with frequent shaking. The solution was cooled to 0°, and the precipitated benzoic acid filtered off. The filtrate was extracted with ether, and the aqueous solution concentrated *in vacuo*. The residue was dissolved in water (20 ml.), and again evaporated *in vacuo* to a syrup and kept in a vacuum at 35—40° for a further hour. This procedure was repeated in order completely to remove traces of hydrochloric acid. It was then dissolved with careful warming in 85% ethanol (200 ml.), decolorised with Norite, and filtered. The clear filtrate was warmed in a water-bath to incipient boiling and basified (litmus) with triethylamine. The solution, which on occasions was faintly cloudy, was allowed to cool to room temperature and an excess of absolute ethanol added to incipient precipitation. The mixture was kept at 0° for 2 days during which a white granular precipitate settled. The supernatant liquid was removed by decantation and the precipitate dried (P_2O_5). The crystals were rinsed with absolute ethanol, collected, and kept in a well-stoppered flask. They melted at 175—180° with decomposition. The crude DL-canaline dissolved in ethanol at 70—80° on addition of water; the solution was then filtered through a preheated funnel, absolute ethanol added to cloudiness, and the whole was kept at 0°. The crystals were filtered off and dried (P_2O_5; m. p. 190—195°). The mother-liquor was concentrated to half its volume and to the hot solution were added small amounts of triethylamine and absolute ethanol to cloudiness. Storage at 0° gave a second crop of crystals (total yield, 3·4 g., 85%). The compound gave positive ninhydrin and Jaffe's tests and a red colour with ferric chloride. Paper chromatography gave R_F 0·77 (Found: C, 35·8; H, 7·6; N, 21·0. Calc. for $C_4H_{10}O_3N_2$: C, 35·8; H, 7·5; N, 20·9%).

(b) The acid (IV) (2·5 g.) was refluxed with 10% sulphuric acid (100 ml.) with frequent shaking. The solution was chilled at 0°, freed from benzoic acid by filtration, and extracted with ether. The aqueous solution was diluted, made slightly alkaline with barium hydroxide, filtered, and neutralised with very dilute sulphuric acid. The filtered solution was concentrated *in vacuo*, and the resulting semisolid material dissolved in ethanol and precipitated with light petroleum. The compound (0·9 g., 92%), m. p. 185—200°, gave positive ninhydrin and Jaffe's tests and had R_F 0·77 (Found: C, 35·0; H, 8·0; N, 20·3%).

(c) The ester (II) (11·1 g.) was hydrolysed as described under (a). The syrupy hydrolysate was dissolved in little water and an excess of 5% ethanolic picric acid was added. The solution was heated for 20 min. at near-boiling temperature, filtered through a hot funnel, and kept for 2 days at 0°. The dipicrate (11·0 g., 62%), recrystallised from water, had m. p. 190° (Found: C, 32·3; H, 2·8; N, 19·0. Calc. for $C_{16}H_{16}O_{17}N_8$: C, 32·4; H, 2·7; N, 18·9%).

This dipicrate (5·9 g.) was shaken with 10% sulphuric acid (60 ml.) in a warm-water bath until the liberated canaline dissolved as the hydrogen sulphate, leaving an insoluble precipitate (picric acid). The mixture was cooled and filtered and the dissolved picric acid extracted with ether. DL-Canaline, liberated from the sulphate as described under (b) and purified as described under (a), had m. p. and R_F as above (0·53 g., 40%) (Found: C, 36·0; H, 7·6; N, 21·0%).

5-2′-*Benzamido-oxyethylhydantoin* (V).—To a solution of sodium ethoxide, from sodium (1·5 g.) in absolute ethanol (50 ml.), benzhydroxamic acid (8·9 g.) in absolute ethanol (75 ml.) was added with stirring. A solution of 5-2′-bromoethylhydantoin [4] (10·3 g.) in absolute ethanol (75 ml.) was added and the mixture stirred at 55—60° for 10—12 hr. The solution was then concentrated *in vacuo*, water was added, and the whole extracted continuously with ethyl acetate. The ethyl acetate was removed *in vacuo*, the residue dried (P_2O_5), and the hydantoin (V) (4 g., 30%) was obtained as hygroscopic crystals. The aqueous mother-liquor was evaporated *in vacuo* and the residue extracted with portions of cold absolute ethanol. After evaporation *in vacuo*, repeated treatment with absolute ethanol, and removal of the ethanol a semicrystalline mass was left, which when dried (P_2O_5) yielded a further amount of the *compound* (2·6 g., 20%) (Found: C, 54·0; H, 5·2; N, 16·0. $C_{12}H_{13}O_4N_3$ requires C, 54·7; H, 4·9; N, 15·9%).

DL-α-*Benzyloxycarbonylamino-γ-benzyloxycarbonylamino-oxybutyric Acid* (VI).—To DL-canaline (III) (4 g.) in water (200 ml.) pyridine (40 ml.) was added. To the stirred solution (0°) benzyl chloroformate (12 g.) was added in small portions. Stirring was continued for an

additional hour at 0°, then for another hour at room temperature. The mixture was kept in cold water for several hours until the oil in the emulsion coagulated. The mixture was extracted 7—8 times with ether, and the combined ethereal extracts were dried ($MgSO_4$) and distilled *in vacuo*, to leave a viscous residue of crude di(benzyloxycarbonyl)-DL-canaline. This was dissolved in a large quantity of ether and precipitated with light petroleum as an oil. This was separated and dissolved in ethanol, and the mixture filtered, concentrated *in vacuo*, and cooled. Light petroleum was added, the product separating as an oil. Crystallisation could only be induced by cooling in acetone–carbon dioxide. The *product* was first dried on a porous plate and then in a vacuum over phosphoric oxide, to a glass (8 g., 66%), which gave negative ninhydrin and Jaffe's tests (Found: C, 59·5; H, 5·3; N, 6·9. $C_{20}H_{22}O_7N_2$ requires C, 60·0; H, 5·5; N, 7·0%).

Attempted Preparation of an α-N-Carboxy-anhydride.—Di(benzyloxycarbonyl)-DL-canaline (VI) (4 g.) was shaken with freshly distilled thionyl chloride (15 g.) and warmed to 40°. After 0·5 hr., dry light petroleum was added and the mixture warmed to 40—50°, till the layer beneath the petroleum became homogeneous. The petroleum was removed by decantation and replaced with a fresh portion of the same solvent. The mixture was refluxed at 50—55° for 0·5 hr. The bulk of the petroleum was decanted and the remainder removed in a vacuum. The viscous residue was dissolved in dry ethyl acetate and precipitated with dry light petroleum, then heated at 60—70° *in vacuo* during 2 hr. The product gave negative ninhydrin and Jaffe's tests and contained chlorine. No free α-amino-nitrogen was detected by the Van Slyke method. The crude product was heated *in vacuo* for 3 hr. at 80—90°. The residue solidified in the cold. The compound is insoluble in water, ether, and light petroleum; it dissolves easily in acetic acid, less so in ethanol. It was extracted with several portions of ethanol, and the filtrate decolorised with Norite. The filtered solution was concentrated *in vacuo* and the residue dried (P_2O_5). A semisolid product (1·3 g., 34%) remained. According to its analysis it seemed to be the lactam form of the di(benzyloxycarbonyl)-DL-canaline (2-benzyloxycarbonyl-4-benzyloxycarbonylamino-3-oxo*iso*oxazine) (Found: C, 62·4; H, 5·2; N, 7·3. $C_{20}H_{20}O_6N_2$ requires C, 62·5; H, 5·2; N, 7·3%). This cyclisation is analogous to that of αγ-di(benzyloxycarbonylamino)butyric acid.[5]

DL-*α-Amino-γ-benzyloxycarbonylamino-oxybutyric Acid* (VII).—To DL-canaline (III) (5 g.) in water (150 ml.) pyridine (30 ml.) was added. The mixture was stirred at 0° and benzyl chloroformate (6·4 g.) was added during 0·5 hr. The mixture was stirred with cooling for a further hour, then for 1 hr. at room temperature, and kept at 0° for several hours. It was twice extracted with ethyl acetate and the cooled aqueous layer was shaken with little ethanol and much ether. The ethereal layer was kept at 0°; a small quantity of white crystals was obtained. The aqueous layer was kept at 0° for several days, until crystals separated. The *benzyloxycarbonyl derivative* (6·5 g., 65%) of DL-canaline had m. p. 208—210°: it is fairly soluble in water but insoluble in ethanol and ether (Found: C, 53·7; H, 5·7; N, 10·4. $C_{12}H_{16}O_5N_2$ requires C, 53·7; H, 6·0; N, 10·4%).

DL-*γ-Benzyloxycarbonylamino-oxy-α-carboxyaminobutyric Anhydride* (VIII).—The acid (VII) (5·4 g.) was dispersed in dry dioxan (75 ml.) at 40—45° and stirred vigorously whilst carbonyl chloride, dried over sulphuric acid, was passed through it for 20—25 min. after complete dissolution. The solvent was removed *in vacuo* at 50—55°, and the residue dissolved in ethyl acetate and precipitated with light petroleum. The supernatant layer was removed by decantation and the process repeated as above. The residual *anhydride* dried (P_2O_5) to a viscous oil (4 g., 68%) [Found: C, 52·2; H, 4·7; N (Van Slyke), 4·8, (Kjeldahl) 9·5. $C_{12}H_{14}O_6N_2$ requires C, 53·0; H, 4·8; N, 4·8, 9·6%].

Poly-(DL-*α-amino-γ-benzyloxycarbonylamino-oxy-butyric Acid*) (IX).—The anhydride (VIII) (2·7 g.) was heated for 3 hr. in a vacuum at 60—90°. Carbon dioxide was evolved, and the material became viscous, finally spongy. The product was yellow-brown, translucent, and insoluble in water and other usual solvents, but dissolved in a great excess of dimethylformamide. Because of its extreme insolubility its chain length could not be determined. A biuret colour was not easily distinguishable owing to the colour of the polymer itself. The *polymer* (1·8 g., 72%) softened above 200° and darkened with decomposition above 250° [Found: C, 57·2; H, 5·8; N, 10·8. $(C_{12}H_{14}O_4N_2)_n$ requires C, 57·6; H, 5·6; N, 11·2%].

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[5] Wilkinson, *J.*, 1951, 104.

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326. *The Dissociation Constants of the Isomeric (−)-Ephedrinium and (+)-ψ-Ephedrinium Ions in Water from 0° to 60°.*

By D. H. Everett and J. B. Hyne.

The thermodynamic acid dissociation constants from 0° to 60° of the positive ions of the isomeric amino-alcohols, (−)-ephedrine and (+)-ψ-ephedrine in water have been determined by an e.m.f. method. The changes in the thermodynamic parameters accompanying the dissociations have been calculated. They are discussed in relation to the stereochemistry of the ephedrine molecules and their positively charged ions, and compared with the corresponding changes for other positively charged (Brönsted–Lowry) acids.

The method of Everett and Wynne-Jones[1,2] for determining the thermodynamic dissociation constants of positively charged acids at a series of temperatures has been extended to the positively charged isomeric (−)-ephedrinium and (+)-ψ-ephedrinium ions in water. The method involves the use of cells with liquid-junction potentials, and the results are analysed in a manner similar to that established in previous papers.[1,2,3]

Experimental

The cells and methods of measurement of e.m.f. were identical with those of Everett, Landsman, and Pinsent.[4] The initial equilibrium in the cells was established at 0° some four hours after commencement of the hydrogen flow. Readings of e.m.f. were normally made at 10° intervals from 0° to 60°, but a few intermediate determinations were made at the lower temtemperatures. 10—12 Hours were required to cover the whole temperature range. Readings were generally reproducible to within ±0·10 mv, although the overall consistency was less satisfactory than in work with simpler amines. After the system had been heated to 60°, the e.m.f.s at lower temperatures were reproduced, showing that no irreversible changes (and in particular no reduction at the hydrogen electrode) occurred during the experiment.

The experimental cell was:

H_2–Pt	Ephedrine hydrochloride [Eph,HCl] (c_3) Ephedrine [Eph] (c_1) KCl (c_2)	KCl (sat.)	HCl (c_4) KCl (c_2)	H_2–Pt

In all cells $c_1 = c_2 = c_4 = c$ = stoicheiometric concentration and $c_2 = (I - c)$ where I = ionic strength.

Materials and Preparation of Solutions.—*(−)-Ephedrine.* Anhydrous (−)-ephedrine was obtained by distilling (−)-ephedrine hemihydrate (from B.D.H.) ($[\alpha]_D^{20}$ +15·5° in H_2O; −4·7° in EtOH) ($[\alpha]_D^{20}$ values are based on weight of ephedrine contained in the hemihydrate) under vacuum and collecting the distillate in a tared flask (b. p. 106—108°/0·5 mm.). A measured volume of hydrogen-saturated conductivity water was added, and after carbon dioxide-free hydrogen had been bubbled through the solution for several hours, it was titrated with standard hydrochloric acid.

(+)-ψ-Ephedrine. (+)-ψ-Ephedrine (from Messrs. Hopkin and Williams Ltd.) was recrystallised once from water and dried by vacuum-desiccation. Its purity (99·7 ± 0·3%) was checked by titration of a weighed amount dissolved in water, and confirmed by measurement of optical rotation ($[\alpha]_D^{20}$ +40·0° in H_2O; +53·0° in EtOH). Solutions were prepared from weighed samples of the recrystallised solid.

Potassium chloride. "AnalaR" potassium chloride was recrystallised from conductivity water, with hot filtration, dried at 140° for 16 hr., and stored over freshly dried silica gel.

Hydrochloric acid. A stock solution of hydrochloric acid was prepared from constant-boiling acid and conductivity water saturated with hydrogen. The acid was stored in a Jena-glass bottle attached to a burette-dispenser. Accurate determination of the normality was made by gravimetric analysis for chloride.

[1] Everett and Wynne-Jones, *Proc. Roy. Soc.*, 1938, *A*, **169**, 190.
[2] *Idem, ibid.*, 1941, *A*, **177**, 499.
[3] Everett and Pinsent, *ibid.*, 1952, *A*, **215**, 416.
[4] Everett, Landsman, and Pinsent, *ibid.*, p. 403.

Solutions were made up immediately before use with water having a specific conductivity less than $1{\cdot}0 \times 10^{-6}$. Solutions of the free base were half-neutralised with hydrochloric acid, and weighed amounts of potassium chloride added to bring the ionic strength to the required value. Calibrated Pyrex flasks and Grade A burettes were used. To minimise atmospheric contamination, solutions were transferred to the cells in the presence of a stream of pure hydrogen.

Results

Twenty-four solutions (twelve for each ephedrine) of various ionic strengths (I) and buffer concentrations (c) were studied over the temperature range 0—60°. In three runs the e.m.f.s differed from those expected by more than 5 mv and these results were rejected. The e.m.f.s at round temperatures were obtained by interpolation over small temperature intervals from large-scale graphs, and from them the apparent equilibrium concentration products, $K^{c\prime}$, of the dissociation $EphH^+ + H_2O \rightleftharpoons Eph + H_3O^+$ were calculated as described previously.[2] Hydrolysis of the amino-alcohol was neglected, as the correction term was small in comparison with the accuracy of the results. The values of $-\log K^{c\prime}$ are given in Tables 1 and 2. The consistency of results within any one run was much better than the reproducibility in successive runs.

Table 1. $-\log K^{c\prime}$ *at various ionic strengths and buffer concentrations for cells containing* (−)-*ephedrine.*

		$-\log K^{c\prime}$						
I	c	0°	10°	20°	30°	40°	50°	60°
0·30	0·040	10·3730	10·0722	9·7861	9·5131	9·2519	9·0009	8·7532
	0·030	10·3606	10·0603	9·7722	9·4966	9·2260	8·9642	8·7063
	0·020	10·3832	10·0821	9·7958	9·5244	9·2659	9·0190	8·7831
	*0·000	10·354	10·048	9·767	9·493	9·236	8·980	8·735
0·20	0·060	10·3592	10·0634	9·7785	9·5074	9·2505	9·0080	—
	0·050	10·3587	10·0554	9·7667	9·4928	9·2338	8·9883	—
	0·030	10·3370	10·0370	9·7526	9·4828	9·2252	8·9778	8·7397
	0·020	10·3380	10·0390	9·7562	9·4870	9·2293	8·9820	8·7450
	*0·000	10·320	10·022	9·737	9·469	9·209	8·968	8·726
0·10	0·030	10·3079	10·0199	9·7397	9·4726	9·2125	—	—
	0·020	10·2986	10·0043	9·7246	9·4562	9·1985	—	—
	0·010	10·2881	9·9917	9·7110	9·4410	9·1796	8·9259	—
	*0·000	10·283	9·992	9·710	9·443	9·184	—	—

* Extrapolated values.

Table 2. $-\log K^{c\prime}$ *at various ionic strengths and buffer concentrations for cells containing* (+)-*ψ-ephedrine.*

		$-\log K^{c\prime}$						
I	c	0°	10°	20°	30°	40°	50°	60°
0·30	0·030	10·5559	10·2441	9·9504	9·6723	9·4069	9·1547	8·9146
	0·020	10·5615	10·2494	9·9563	9·6788	9·4142	9·1634	8·9226
	0·010	10·5488	10·2403	9·9483	9·6705	9·4073	9·1567	8·9205
	0·005	10·5255	10·2142	9·9216	9·6435	9·3791	9·1286	8·8897
	*0·000	10·552	10·240	9·947	9·672	9·404	9·163	8·914
0·20	0·030	10·5173	10·2187	9·9271	9·6405	9·3737	9·1179	8·8707
	0·020	10·5163	10·2102	9·9185	9·6426	9·3791	9·1269	8·8860
	0·010	10·5308	10·2215	9·9299	9·6538	9·3917	9·1404	8·8950
	0·005	10·5073	10·1964	9·9005	9·6181	9·3451	9·0749	8·8111
	*0·000	10·514	10·208	9·915	9·636	9·371	9·123	8·883
0·10	0·020	10·4688	10·1675	9·8795	9·6068	9·3490	9·1001	8·8557
	0·010	10·4905	10·1841	9·8946	9·6202	9·3607	9·1095	8·8625
	0·005	10·4735	10·1646	9·8749	9·5994	9·3334	9·0710	—
	*0·000	10·475	10·169	9·882	9·604	9·345	9·099	8·854

* Extrapolated values.

In the usual method of analysis of results [2] liquid-junction effects are eliminated by extrapolation at each ionic strength to zero buffer concentration, and the thermodynamic dissociation

constants are obtained by extrapolation to zero ionic strength. The heat, heat capacity, and entropy changes associated with the equilibrium at infinite dilution are then calculated from the temperature dependence of the thermodynamic dissociation constants by using, for example, the equation:

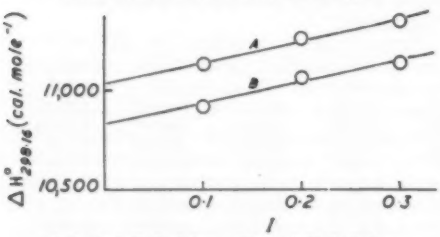
$$\log K = A/T + B \log T + C \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $A = \Delta H_0^\circ/2{\cdot}303\boldsymbol{R}$, $B = \Delta C_p^\circ/\boldsymbol{R}$, and $C = (\Delta S_0^\circ - \Delta C_p^\circ)/2{\cdot}303\boldsymbol{R}$.[5]

This procedure, using the method of least squares with Gauss multipliers,[6] was followed in the first analysis. However, the lower reproducibility achieved in the present work, compared with that on simple amines, made it difficult to ensure that the heat and heat-capacity values were not influenced by systematic errors introduced in the extrapolations. To eliminate this uncertainty, a second analysis was made in which the results of each individual run were analysed by the method of Everett and Wynne-Jones.[5] It was found that for a given ephedrine B did not vary systematically with either I or c; the mean values were $+10{\cdot}9$ and $+9{\cdot}0$ for (−)-ephedrine and (+)-ψ-ephedrine respectively, with standard deviations of the mean of $\pm 0{\cdot}8$ and $\pm 0{\cdot}3$. Rounded values of 11·000 and 9·000 were used in the subsequent analysis. It was then found that at a given ionic strength A showed no regular variation with c; but the mean values of A at fixed ionic strength varied linearly with I, and enabled A at infinite dilution to be obtained by extrapolation. The values of $\Delta H^0_{298{\cdot}16}$ corresponding to the values of A and B are shown as a function of ionic strength in Fig. 1. Although the standard deviations of ΔH may be as high as ± 60 cal. mole^{-1}, the difference of 200 cal. mole^{-1} between the results for the two ephedrines is observed at each ionic strength, and indicates that this difference is real. A similar conclusion had been reached in the first analysis.

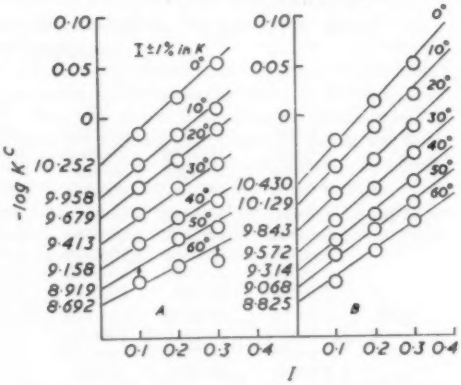
The constant C was then obtained by inserting the values of log K extrapolated to infinite dilution from the first analysis into equation (1) with the appropriate values of A and B; the mean value of C was found and on insertion in equation (1) gave a set of " calculated values " of log K. The self-consistency of the analysis is shown by Fig. 2, where the values of log K^c at each ionic strength are plotted against I. The extrapolated values of log K at zero ionic strength are those calculated from the appropriate equation (1), while the slopes of the lines were obtained in the following way. The slope at one temperature [20° for (−)-ephedrine,

FIG. 1. *Variation of heat of dissociation of ephedrinium ions at 25° with ionic strength.*



A, (+)-ψ-*Ephedrine*. *B*, (−)-*Ephedrine*.

FIG. 2. *Classical dissociation constants* (as $-\log K^c$) *of ephedrinium ions as a function of ionic strength at various temperatures.* [*Variation of slope of lines with temperature calculated from data in Fig.* 1, *extrapolated values from equation* (1) *with appropriate constants. Zero of ordinates not fixed; scale of* $-\log K^c$ *given on upper part of ordinates.*]



A, (−)-*Ephedrine*. (*B*), (+)-ψ-*Ephedrine*.

[5] Everett and Wynne-Jones, *Trans. Faraday Soc.*, 1939, **35**, 1380.
[6] Goulden, " Methods of Statistical Analysis," 2nd edn., Wiley, New York, pp. 138—142.

30° for (+)-*ψ*-ephedrine] was taken from the best straight line through the experimental points, and that at other temperatures was calculated from the equation: [2]

$$\frac{\partial}{\partial I}\left(\frac{\Delta H}{RT^2}\right) = \frac{\partial}{\partial T}\left(\frac{\partial \ln K}{\partial I}\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

The variation of ΔH with I was taken from Fig. 1, and equation (2) was then integrated to obtain the slopes d log K/dI at other temperatures. Apart from a few results for (−)-ephedrine at 50° and 60°, the internal consistency of the analysis is better than ±1% in K. However, the uncertainties in extrapolation to zero buffer concentration may introduce a systematic error up to 2—3% in absolute values of K. The method of analysis ensures, however, that any error influences only ΔG° and not ΔH° and ΔC_p°.

The parameters of equation (1) and thermodynamic functions at 25° are collected in Table 3 while the final values of log K are given in Table 4 where they are compared with previous work.

TABLE 3. *Parameters of equation* (1) *and thermodynamic functions at* 25° *for the dissociation of* (−)-*ephedrinium and* (+)-*ψ-ephedrinium ions in water.*

Parameter and thermodynamic function	(−)-Ephedrinium	(+)-*ψ*-Ephedrinium	Parameter and thermodynamic function	(−)-Ephedrinium	(+)-*ψ*-Ephedrinium
A (degrees)	−942·96	−1246·07	ΔS° (cal. mole^{-1})	−7·35 ± 0·5	−7·42 ± 0·5
B	9·000	11·000	(J mole^{-1})	−30·75 ± 2·0	−31·05 ± 2·0
C	33·601	27·797	ΔC_p° (cal. mole^{-1})	22 ± 4	18 ± 2
ΔG° (cal. mole^{-1})	13,020 ± 15	13,245 ± 10	(J mole^{-1})	92 ± 16	75 ± 9
(J mole^{-1})	54,475 ± 60	55,420 ± 40			
ΔH° (cal. mole^{-1})	10,830 ± 80	11,030 ± 80			
(J mole^{-1})	45,310 ± 350	46,150 ± 350			

(The limits given are approximately twice the standard deviations of the means.)

TABLE 4. *Thermodynamic dissociation constants of ephedrinium ions* (−log K_a).

Temp.		0°	10°	17·6°	20°	22°	25°	30°	31°	38°	40°	50°	60°
(−)-Ephedrinium	(*a*)	10·252	9·958	9·745	9·679	9·625	9·544	9·413	9·387	9·213	9·158	8·919	8·692
	(*b*)		9·942	9·720			9·522		9·364	9·205			
	(*c*)					9·58 †	9·58 ‡						
(+)-*ψ*-Ephedrinium	(*a*)	10·430	10·139		9·843	9·787	9·706	9·572			9·314	9·068	8·833
	(*c*)					9·74 †							

(*a*) Calc. from equation (1) with values of A, B, and C from Table 3. (*b*) Values from Äyräpää.[7] (*c*) Other values: † Prelog and Häfliger [8]; ‡ Leffler, Spencer, and Burger.[9]

Äyräpää [7] has determined the dissociation constant of the (−)-ephedrinium ion in water, using a hydrogen–calomel electrode cell with liquid junctions over the temperature range 10—38°. In this range our values of K_a are on the average 4% lower than his. Other workers report figures at a single temperature [8,9] and, despite the fact that they do not appear to have made a correction for ionic strength, the agreement with the present work is reasonably good. For (+)-*ψ*-ephedrine only a single value at 22° due to Prelog and Häfliger [8] is available; the agreement with the present determination is only fair.

Discussion of thermodynamic functions

The thermodynamic functions for the dissociation of positively charged acids have been discussed by Everett and Wynne-Jones,[2,5] Everett and Pinsent,[3] Evans and Hamann,[10] and by Everett.[11] The results of the present work can be discussed in essentially similar terms; the relevant data are given in Table 5.

We find that the entropies of dissociation of the two ephedrinium ions (which are secondary ammonium ions) are identical (−7·4 cal. deg.$^{-1}$ mole^{-1}) and lie between values

[7] Äyräpää, *Svensk Kem. Tidskr.*, 1950, **62**, 135.
[8] Prelog and Häfliger, *Helv. Chim. Acta*, 1950, **33**, 2021.
[9] Leffler, Spencer, and Burger, *J. Amer. Chem. Soc.*, 1951, **73**, 2612.
[10] Evans and Hamann, *Trans. Faraday Soc.*, 1951, **47**, 34.
[11] Everett, *Ind. Chim. belge*, 1951, **16**, 647.

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characteristic of simple secondary (*e.g.*, dimethylammonium $\Delta S^0 = -9{\cdot}5$) and primary (*e.g.*, methylammonium, $\Delta S^0 = -4{\cdot}7$) ammonium ions, while the heat-capacity changes

TABLE 5. *Thermodynamic functions for the dissociations of some positively charged acids in water at 25°.*

Acid	ΔG^0 (cal. mole^{-1})	ΔH^0 (cal. mole^{-1})	ΔS^0 (cal. deg.$^{-1}$ mole^{-1})	ΔC_p^0 (cal. deg.$^{-1}$ mole^{-1})	Ref.
Ammonium	12,562	12,400	− 0·5	0·0	1, 12
Methylammonium	14,484	13,092	− 4·7	+ 7·5	2, 5
Ethylammonium	14,500	13,580	− 3·1	—	10
Propylammonium	14,360	13,850	− 1·7	~+ 8	10, *a*
Butylammonium	14,450	14,070	− 1·3	~+ 9	10, *a*
Dimethylammonium	14,721	11,880	− 9·5	+19·0	2, 5
Trimethylammonium	13,384	8,828	−15·3	+41·0	2, 5
2-Hydroxyethylammonium	12,960	12,090	− 2·9	− 1·2	*b*
(−)-Ephedrinium	13,020	10,830	− 7·4	+22	This work
(+)-ψ-Ephedrinium	13,245	11,030	− 7·4	+18	This work

a, Landsman, unpublished work. *b*, Bates and Pinching, *J. Res. Nat. Bur. Stand.*, 1951, **46**, 349.

are also nearly identical (22 and 18 cal. deg.$^{-1}$ mole^{-1}) and are within experimental error equal to the value characteristic of a simple secondary amine (*e.g.*, dimethylammonium, $\Delta C_p = +19$).

The less negative value of ΔS, compared with that of dimethylammonium, may be evidence for a " chain stiffening " effect in the ion, perhaps (see below) associated with restricted rotation in the molecule: we have postulated previously [4] that this influences ΔS much more than ΔC_p. The magnitude of the change is comparable with that observed on passing from the methyl group of methylammonium to the three-carbon chain of propylammonium. The hydroxyl group might, on general grounds, be expected to influence ΔS; but the data for ethylammonium and 2-hydroxyethylammonium suggest that this is not a large effect. That the heat-capacity changes are the same as that for dimethylammonium suggests an almost exact balancing of the effect of introducing additional hydrocarbon substituents near the charge centre, which according to our previous views [4] causes a substantial increase in ΔC_p, and that of the hydroxyl group, which from a comparison of hydroxyethylammonium with other primary amines decreases ΔC_p. If the slightly smaller value for ΔC_p for (+)-ψ-ephedrinium is real, this indicates that in its influence on the solvent the hydroxyl group competes more effectively with the hydrocarbon constituents in the ψ-ephedrine conformation; if, as suggested below, the *N*-methyl group and the hydroxyl group are adjacent in the ψ-ephedrine molecule this effect would be not unexpected.

Because of the similarity between the entropy and the heat-capacity changes of dissociation of the two ephedrine ions, the difference in acid strength [$\delta(\Delta G^0) = 225$ cal. mole^{-1}] is, within the experimental accuracy, attributable to the difference between the heats of dissociation [$\delta(\Delta H^0) = 200$ cal. mole^{-1}]. Consequently our discussion of acid strengths can be limited to a consideration of energy terms. We shall interpret our results on the assumption that the isomeric ephedrine molecules differ in the relative dispositions of the hydroxyl and methylamino-groups, while in the isomeric ions these groups are similarly disposed.

Chemical evidence, concerned mainly with the ease of formation of derivatives of ephedrine and ψ-ephedrine, suggests that transition states in which the hydroxyl and methylamino-groups are spatially adjacent are more readily formed by the ψ-ephedrines than by the ephedrines.[13] This appears reasonable from a study of molecular models

[13] Everett and Landsman, *Trans. Faraday Soc.*, 1954, **50**, 1221.

[13] Hyne, Ph.D. Thesis, St. Andrews, 1954; Close, *J. Org. Chem.*, 1950, **15**, 1131; Nagai and Kanao, *Annalen*, 1929, **470**, 157; Fodor and Koczka, *J.*, 1952, 850; Welsh, *J. Assoc. Offic. Agric. Chem.*, 1948, **31**, 528; Földi, Földi, and Földi, *Chem. and Ind.*, 1955, 1297.

(Catalin pattern) and is confirmed by approximate calculations we have made of the energetically most favourable conformations, based on a consideration of repulsive interactions between non-bonded atoms and ignoring specific attraction between hydroxyl and methylamino-groups. If we define the conformation by the angle between the planes $C_\beta C_\alpha O$ and $NC_\beta C_\alpha$ (Fig. 3), then in accordance with the generally accepted view [14] the most stable conformations are the staggered orientations at 180° for ephedrine (E_{180}) and 60° for ψ-ephedrine (ψ_{60}). Other, less marked, energy minima are found at 60° (E_{60}) and (E_{300}) for ephedrine, and at 180° (ψ_{180}) and 300° (ψ_{300}) for ψ-ephedrine. The interaction

FIG. 3. *The staggered conformations of ephedrine and ψ-ephedrine.* [(+)-*Ephedrine and* (+)-ψ-*ephedrine are shown*]. *Underlined conformations are probable conformations of neutral molecules.*

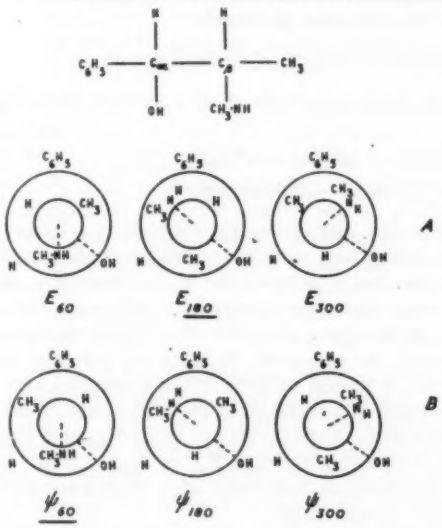
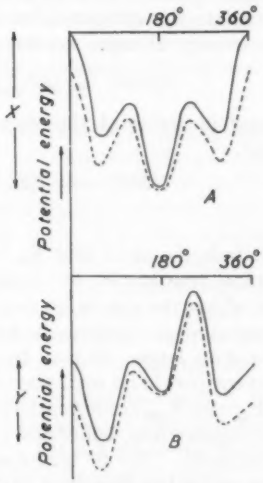


FIG. 4. *Schematic potential energy curves for rotation about the* $C_\alpha C_\beta$ *bond in* (*A*) *ephedrine and* (*B*) ψ-*ephedrine.*



(———) *Ignoring dipole interaction between* OH *and* NHMe.
(– – – –) *Showing probable influence of dipole interaction between* OH *and* NHMe.

curves are shown schematically in Fig. 4. It is difficult to estimate quantitatively the effect of attractive interactions between hydroxyl and methylamino-groups, but the direction in which they would modify the curves is indicated by the broken lines.

It seems unlikely that the most stable conformations of the ephedrinium ions will be the same as those of the corresponding neutral molecules. Ion-dipole interaction between $Me{\cdot}NH_2^+$ and OH will tend to bring these groups together in *both* ions, and may well overwhelm the steric repulsions. Both ions will probably approximate to the 0° conformation, and this may be further stabilised by hydrogen bonding with solvent water. There is no direct evidence for these conclusions, but Phillips [15] has shown by *X*-ray structure analysis that the $Me{\cdot}NH_2^+$ and OH groups are adjacent in (−)-ephedrinium hydrochloride crystals, while recent measurements of the magneto-optic effect by Fleming and Saunders [16]

[14] Brown, McDaniel, and Häfliger in " Determination of Organic Structures by Physical Methods," ed. Braude and Nachod, Interscience Publ. Inc., 1955, p. 654.
[15] Phillips, *Acta Cryst.*, 1954, **7**, 159.
[16] Fleming and Saunders, *J.*, 1955, 4150.

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can be interpreted as supporting the view that the two positive ions have similar conformations in aqueous solutions. If we assume that both ions have the 0° conformation, and denote the most stable conformations of the neutral molecules by E_m and ψ_m respectively, then the ionisation processes can be represented formally as follows:

$$EH_0^+ \longrightarrow E_0 + H^+ \longrightarrow E_m + H^+ \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$\psi H_0^+ \longrightarrow \psi_0 + H^+ \longrightarrow \psi_m + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$\Delta G^0(\text{diss}) \qquad \Delta G^0(\text{rot})$$

The overall free-energy change of the reaction is thus the sum of two terms, the first $[\Delta G^0(\text{diss})]$ referring to the dissociation of the proton while the molecule is retained in the 0° conformation, and the second $[\Delta G^0(\text{rot})]$ to the rotation of the molecule to its most stable form. It is then reasonable to suppose that the first stages are identical from an electrostatic point of view for both ions,* so that we can equate $\Delta G^0(\text{diss})$ for the two ions and attribute the difference between the ionisation constants to the difference between the free-energy changes accompanying the rotation processes:

$$\delta(\Delta G^0) = \Delta G^0(E) - \Delta G^0(\psi) = \Delta G^0(\text{rot})(E) - \Delta G^0(\text{rot})(\psi)$$

Expressed in terms of the standard chemical potentials of the various conformations we have:

$$\left.\begin{aligned}\delta(\Delta G^0) &= [\mu^0(E_m) - \mu^0(E_0)] - [\mu^0(\psi_m) - \mu^0(\psi_0)] \\ &= (Y - X) \text{ (see Fig. 4)} = -225 \text{ cal. mole}^{-1}\end{aligned}\right\} \quad . \quad . \quad . \quad . \quad (4)$$

We conclude therefore that E_m is more stable, relative to E_0, than ψ_m is relative to ψ_0. If chemical reaction in, for example, condensation reaction occurs through a transition state in which the ephedrine or ψ-ephedrine has to achieve the 0° conformation, then we shall expect such reactions to be somewhat faster for ψ-ephedrine, although the effects should not be large. It may be noted, furthermore, that the effect of dipole interaction between hydroxyl and methylamino-group is, for ephedrine, to bring the potential energies of the E_{60} and E_{300} conformations down closer to that of E^{180}: if these energies were equal then, at equilibrium, ephedrine would consist of a mixture of the three conformations in equal amounts. The 0° transition state can be formed directly from E_{60} and E_{300}, but E_{180} can reach the transition state only by passing through E_{60} or E_{300}. If the energy barrier separating E_{180} from the other two conformations were high, then a second factor inhibiting the rate of reaction of ephedrine would result.

An interpretation of the relative strengths of the isomeric ephedrinium ions has been given previously by Prelog and Häfliger.[8,14] It is, however, not quite clear from their paper whether they suppose the ions to retain the conformation of the neutral molecules. They state that hydrogen bonding of the hydroxyl and methylamino-groups will tend to occur through the solvent structure, and they attribute the difference in acid strength to the fact that this tendency is favoured by the configuration of (+)-ephedrine and opposed by that of (−)-ephedrine.

One of us (J. B. H.) is indebted to the Council of University College, Dundee, for the award of a Post Graduate Scholarship. We also acknowledge financial assistance from the Chemical Society Research Fund, and from Imperial Chemical Industries Limited.

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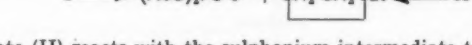
[*Received, November 9th*, 1956.]

* A second-order effect might arise if, for example, the detailed electron-density distribution in a methyl group, and hence its interaction with a proton, were dependent on the nature of the spatially adjacent groups in the molecule.

327. *Reactions of Ethylthioethyl* OO-*Dimethyl Phosphorothioates in Water.*

By D. F. Heath.

A kinetic study shows that *O*-ethylthioethyl *OO*-dimethyl phosphorothionate (I) and *S*-ethylthioethyl *OO*-dimethyl phosphorothiolate (II) decompose in water into phosphorothioate ion and, probably, a cyclic sulphonium ion:



The thiolate (II) reacts with the sulphonium intermediate to a small extent to give an ion, probably $(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Et{\cdot}CH_2{\cdot}CH_2{\cdot}SEt$, which is a powerful, unstable anticholinesterase. Similar reactions take place in the absence of water. The thiolate (II) also decomposes in water by some other mechanism. It is concluded that this is direct attack by water from a comparison of its rate with the rates of hydrolysis of the sulphoxide and sulphone of (II), which cannot give cyclic sulphonium intermediates.

Some reactions in water of *S*-2-ethylthioethyl *OO*-dimethyl phosphorothiolate, $(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SEt$ (II), and *O*-2-ethylthioethyl *OO*-dimethyl phosphorothionate, $(MeO)_2PS{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}SEt$ (I), have been described.[1,2] 1% Suspensions of the thionate in water gave 50% yields of thiolate.[1] In solution [2] (<0·1%), the thionate gave smaller yields of thiolate, non-toxic ionic products, and less than 0·1% of a very powerful, positively charged, unstable anticholinesterase, the yield of which was increased about ten-fold by initial addition of a small amount of thiolate. The thiolate decomposed in water much more slowly than the thionate (half life 10·7 days at 37° against about 10 minutes for the thionate). The main products were non-toxic ions, but two anticholinesterases were produced. One was the methylsulphonium derivative of the thiolate, $(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}EtMe$,[2,3] which had half life in water of 14·4 days at 37°; the other had a half life of 100 min. at 37° and was assumed to be the same as that produced from the thionate. Both were formed at rates proportional to the square of the thiolate concentration. The additional yield of the unstable anticholinesterase obtained on adding thiolate to thionate was not formed from the thiolate alone, as the concentration added was only enough to account for about 1% of the increase.

I now suggest a structure for the unstable anticholinesterase, and, from study of the kinetics of its formation, suggest mechanisms for the decomposition of both the thionate and the thiolate in aqueous solution.

Results

As the reactions are acid-forming, most were carried out in 0·01N-hydrochloric acid, and those with thionate in solutions containing about 5% of ethanol to increase its rate of solution. In preliminary experiments no observable changes in rate were caused by changing the acid concentration to 0·0001N, and the effects of adding ethanol were confined to the beginnings of runs, which were not reproducible in its absence.

The unstable anticholinesterase was not separated pure, so that its concentrations could not be expressed in the usual terms. Therefore they are expressed as the number of times the solution had to be diluted to give a solution inhibiting 50% of sheep erythrocyte cholinesterase under standard conditions. The probable error in their determination was 5% except below 50 units in solutions previously extracted with chloroform to remove non-ionic products. Traces of chloroform lowered the values, and were difficult to remove completely by aeration

[1] Henglein and Schrader, *Z. Naturforsch.*, 1955, **10**, 1.
[2] Heath and Vandekar, *Biochem. J.*, 1957, **67**, 187.
[3] Heath, *Nature*, 1957, **179**, 377.

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without taking so long that significant quantities of anticholinesterase decomposed in the process. Thus, below 50 units, results may be up to 5 units low.

First, it was shown that the unstable anticholinesterases from thiolate and thionate, both separately and mixed, were probably the same, and could be identified with the ethylthioethylsulphonium derivative of the thiolate, $(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Et{\cdot}CH_2{\cdot}CH_2{\cdot}SEt$, which was synthesised in low yield by the action of bromoethyl ethyl sulphide on the thiolate in alcohol, and separated by electrophoresis. All the anticholinesterases were positively charged, and hydrolysed in water according to first-order kinetics at very similar rates, as shown in Table 1.

TABLE 1. *First-order constants for the hydrolysis at 21·8° of the unstable anticholinesterase.*

From	PS	PS + PO	PO	Synthesis
10^3k (min.)	1·24 ± 0·04	1·33 ± 0·02	1·32 ± 0·05	1·35 ± 0·05
,, ...	1·26 ± 0·02	1·37 ± 0·02	1·28	—

PS, from thionate; PS + PO, from thionate–thiolate; PO, from thiolate. Errors are standard errors.

The minor differences, barely exceeding the standard errors, might be due to slight catalytic effects, as the samples contained different amounts of other ions. The reasonable assumption that the compounds are the same is justified by later kinetic work. Their structure is fixed almost unambiguously by the method of synthesis and their positive charge, the only doubt being as to which of the two sulphur atoms carries the positive charge.

The kinetic results for solutions of thionate, with and without added thiolate, are given in Tables 2—6.

Tables 2 and 3 show the concentrations of anticholinesterase obtained in typical runs. With thionate alone, the rate of formation was initially slow, and then rose rapidly to a maximum. Mixtures of thiolate and thionate however gave the anticholinesterase rapidly from the start, and a much higher concentration from a lower initial concentration of thionate. After the times shown the concentrations fell as the anticholinesterase decomposed.

TABLE 2. *Anticholinesterase from thionate alone at* 21·8°.

	Time (min.)	10	21	49	76	100	141
A	Anticholinesterase, found	4	21	129	269	318	400
	Anticholinesterase, calc.	6	26	126	241	316	409
	Time (min.)	12	20·5	40	62	95	124
B	Anticholinesterase, found	11	33	155	346	595	778
	Anticholinesterase, calc.	11	40	158	331	573	740

A, 0·314 mg. of thionate/ml.; *B*, 0·411 mg. of thionate/ml.

TABLE 3. *Anticholinesterase from thionate + thiolate at* 21·8°.

	Time (min.)	0·8	7·0	14·2	26·3	53·8	75·5	124	
A	Anticholinesterase, found...	66	707	1200	1900	3580	3800	4720	
	Anticholinesterase, calc. ...	87	701	1320	2170	3400	3980	4660	
	Time (min.)	1·2	6·2	12·2	20·0	40·0	60·0	80·4	100
B	Anticholinesterase, found...	124	699	1202	1910	3430	4000	4810	5870
	Anticholinesterase, calc. ...	135	661	1220	1850	3110	3990	4640	5260

A, 0·231 mg. of thionate/ml. + 0·333 mg. of thiolate/ml.; *B*, 0·205 mg. of thionate/ml. + 0·395 mg. of thiolate/ml.

Table 4 shows the maximum concentrations of the unstable anticholinesterase given by various concentrations of the thionate alone at 21·8°. These maximum concentrations are apparently proportional to $P_0^{2\cdot42}$, where P_0 is the initial concentration of the thionate.

Table 5 shows that, for thionate–thiolate, the concentration of anticholinesterase produced in the first 14 minutes was proportional to the thiolate concentration, when the initial thionate concentration was constant. At this time the conversion of thionate to thiolate had not gone far enough to affect the results.

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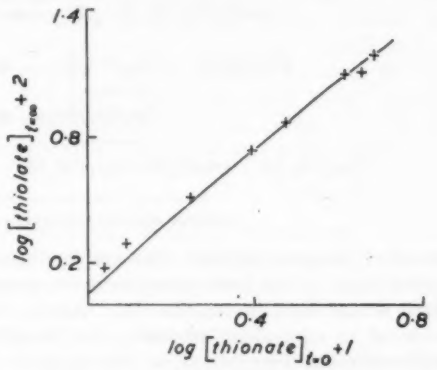
Within the error on the thiolate determinations (about 5%) a log–log plot of the final concentrations of thiolate produced in runs with various initial concentrations of thionate is linear (see Figure): log $[\text{thiolate}]_\infty$ = 1·6 log P_0 + constant.



Points are experimental, curve is theoretical.

The concentrations of ionic phosphates at various times in a solution of thionate alone are given for a typical run in Table 6.

TABLE 4. *Maximum yield of anticholinesterase from thionate alone at* 21·8°.

Thionate (mg./ml.)	0·360	0·276	0·181	0·090
Anticholinesterase	625	343	119	21
$P_0^{1\cdot42}$ × constant	638	336	119	22

TABLE 5.

Thiolate (mg./ml.)	0·348	0·174	0·087
Anticholinesterase	1215	676	333
Anticholinesterase/[thiolate]	3490	3890	3830

Thionate concentration = 0·211 mg./ml. throughout.

TABLE 6. *The percentage of total phosphorus as ions at various times in a solution of thionate initially of* 0·411 *mg./ml. at* 21·8°.

Time (min.)	1·1	6·0	12·0	20·5	40·0	62·0	95·0
%, found	0·7	7·5	14·1	23·4	36·7	47·3	59·0
%, calc.	1·6	8·3	15·1	23·3	37·1	47·4	57·0

The anticholinesterase contributed a negligible amount to these concentrations. Curves drawn through these and other results indicate a short induction period of about 0·7 min., after which they rise smoothly. I have assumed that this period is required to complete the solution or solvation of the thionate, and ignore it in the following discussion.

DISCUSSION

In trying to find a sequence of reactions which fits the results, several were tried which failed. As these are new, they are described briefly in the experimental section. A satisfactory sequence was found by considering the suggestion [4] that the isomerisation of the diethyl homologue of the thionate may go *via* an ionic intermediate:

$$(EtO)_2PS{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}SEt \longrightarrow (EtO)_2PO{\cdot}S^-{\cdot}\overset{+}{C}H_2{\cdot}CH_2{\cdot}\overset{+}{S}Et$$

This seems to have been vizualised as an ion pair, which does not fit my results. If,

[4] Fukuto and Metcalf, *J. Amer. Chem. Soc.*, 1954, **76**, 5103.

however, it is assumed that the phosphorothioate and dimethylene-ethylsulphonium ions separate, and that the latter is unstable, the following reactions may be written:

$$(MeO)_2PS{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}SEt \xrightarrow{k_1} (MeO)_2PO{\cdot}S^- + CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Et \quad . \quad . \quad . \quad . \quad (1)$$

$$(MeO)_2POS^- + CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Et \xrightarrow{k_2} (MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SEt \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Et \xrightarrow{k_3} \text{products} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Et + (MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SEt \xrightarrow{k_4} \text{unstable anticholinesterase} \quad . \quad . \quad . \quad (4)$$

$$\text{unstable anticholinesterase} \xrightarrow{k_5} \text{non-toxic products} \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Dimethyl phosphorothioate ions are produced by reaction (1). If k_2 and k_3 are much greater than k_1, the ionic phosphorus compounds found consist of that phosphorothioate which is not used in reaction (2). As the sulphonium and phosphorothioate ions are produced in equivalent amounts, the phosphorothioate remaining is equivalent to the sulphonium ion decomposed, so that equation (3) also represents the rate of accumulation of ions containing phosphorus. With the constants given in Table 8, the correct dependence of the maximum concentration of thiolate on the initial concentration of thionate is found (see Figure), and the calculated concentrations of ionic phosphates, and of unstable anticholinesterase from solutions of thionate, both with and without added thiolate, agree with those found, as shown in Tables 6, 2, and 3. In Table 6 the agreement is poor at the beginning, where the induction period affects the results. In Tables 2 and 3 the theoretical results are roughly corrected for hydrolysis of the anticholinesterase, and are correct to within 2%.

It follows from the proposed scheme that adding *OO*-dimethyl phosphorothioate to a solution of the thionate at the start of a run should increase the yield of thiolate on thionate by favouring reaction (2) over reaction (3). In such an experiment the yield was increased from 24·5% to 84·6%. The yield calculated from the rate equations is 82·2%, agreeing within experimental error.

The thiolate alone in water also gave the unstable anticholinesterase. As the thiolate is much more stable than the anticholinesterase, the latter reached a concentration after a few hours at 37° which changed only slowly. In Table 7 this concentration is shown to be proportional to the square of the thiolate concentration. The formation of the anticholinesterase can be explained if reaction (2) is reversible:

$$(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SEt \xrightarrow{k_6} (MeO)_2PO{\cdot}S^- + CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Et \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

Near the beginning of the reaction the concentration of the thiophosphate ion is small, so the reverse of reaction (6) can be ignored. Also, k_6 is very much smaller than the other constants. Then $[A] = k_5k_6[PO]^2/k_3k_4$, in accordance with the observed proportionality.

TABLE 7. *Unstable anticholinesterase from thiolate alone at* 37°.

Thiolate (mg./ml.)	7·52	4·51	3·01
Anticholinesterase, found	14,250	4,840	2,080
Anticholinesterase/[thiolate]^2	252	238	230

The constants for thionate–thiolate mixtures at 37° were also determined, and are shown in Table 8. From these, and the results in Table 7, k_6 at 37° is found to be $3{\cdot}05 \times 10^{-5}$ min.$^{-1}$, which represents the rate of decomposition in water of the thiolate by the above mechanism. The overall rate of decomposition at infinite dilution, where the reactions giving anticholinesterases do not contribute, is represented by the constant

$4{\cdot}18 \times 10^{-5}$ min.$^{-1}$, so that apparently some decomposition, represented by $k = 1{\cdot}13 \times 10^{-5}$ min.$^{-1}$, takes place by some other mechanism.

Now the sulphoxide and sulphone of the thiolate, $(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SO{\cdot}Et$ and $(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SO_2{\cdot}Et$, cannot give the cyclic sulphonium intermediate, yet they hydrolyse in dilute acids. It seems likely that the hydrolysis rates of the thiolate, its sulphoxide, and its sulphone should form a continuous series, as successive oxidation of the side-chain should increase inductive effects. The first-order rate constants for the sulphone and sulphoxide are $2{\cdot}60 \pm 0{\cdot}01 \times 10^{-5}$ min.$^{-1}$ and $2{\cdot}18 \pm 0{\cdot}01 \times 10^{-5}$ min.$^{-1}$, which do form such a series with $1{\cdot}13 \times 10^{-5}$ min.$^{-1}$ for the thiolate. Thus the value of this constant suggests that the thiolate is directly attacked by water to some extent:

$$(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SEt + H_2O \xrightarrow{k_7} \text{ionic products} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Water does not take a direct part in the decomposition of the thionate and thiolate *via* the cyclic intermediate. Thus a stored dry sample of the thionate contains thiolate, ionic products, and anticholinesterases.[2] Some rough experiments on the dry thiolate show that it is less stable than the sulphoxide, which is already known to be much more stable than the sulphone, as it is reduced to the thiolate when heated.[2]

The scheme explains why the rate constant for the decomposition of thiolate in water decreased with time, especially at higher concentrations.[2] As *OO*-dimethyl hydrogen phosphorothioate is relatively stable, its concentration increases as the reaction proceeds, until the reverse of reaction (6) becomes important.

From the rate constants at different concentrations of the thiolate alone the I_{50} of the unstable anticholinesterase is calculated to be $1{\cdot}4 \times 10^{-9}$M. The value found directly is $6{\cdot}9 \times 10^{-9}$M, but is likely to be high.

The account of the reactions of the thiolate and thionate in water is completed by adding those for the formation and decomposition of the stable inhibitor:

$$2(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SEt \xrightarrow{k_8} (MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}EtMe + MeO{\cdot}PO_2^-{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}SEt \quad (8)$$

$$(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}EtMe \xrightarrow{k_9} \text{non-toxic products} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

These have been discussed elsewhere.[2,3]

The constants for all nine reactions are given in Table 8. The ratio k_3/k_5 is given in terms of the I_{50} value of the unstable anticholinesterase. The results are very insensitive to k_3/k_2, changes of 10% barely affecting them.

TABLE 8. *Rate constants.*

	10^2k_1	$10^2k_3/k_2$	$10^8I_{50}k_3/k_5$	10^5k_6	10^5k_7	10^4k_8	10^3k_4	10^5k_9
37·0°	7·5	1·93	7·89	3·05	1·13	6·5	7·0 *	3·7 *
21·8°	1·5	1·52	4·61	—	—	—	1·3	—

All constants are in min. mole l.$^{-1}$ units. * Taken from Heath and Vandekar.[2]

EXPERIMENTAL

Determinations of Anticholinesterase Activity.—Such determinations were carried out as described by Heath and Vandekar.[2]

Phosphorus Analyses.—Phosphorus in samples was determined after combustion to phosphate [5] except that a little bromine water was added before ashing to avoid evaporation losses.[6]

O-2-*Ethylthioethyl* OO-*Dimethyl Phosphorothionate, and* S-2-*Ethylthioethyl,* S-2-*Ethylsulphinylethyl, and* S-2-*Ethylsulphonylethyl* OO-*Dimethyl Phosphorothiolates.*—For the sources and careful purification of these compounds, see Heath and Vandekar.[2]

Potassium OO-*Dimethyl Phosphorothioate.*—*OO*-Dimethyl *p*-nitrophenyl phosphorothionate was hydrolysed with ethanolic potassium hydroxide, acidified to pH 4 with hydrochloric acid, the product diluted with water, and the solution extracted six times with chloroform. The

[5] Fiske and Subbarow, *J. Biol. Chem.*, 1925, **66**, 375.
[6] Gardner and Heath, *Analyt. Chem.*, 1953, **25**, 1849.

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aqueous layer was made slightly alkaline and concentrated to dryness *in vacuo*. The crude product, containing potassium chloride, gave no precipitate with barium chloride in the cold, and a copious one when heated with concentrated nitric acid for a few minutes. Analysis [7] gave thiophosphate equivalent to 63% of the phosphorus present.

2-Ethylthioethylsulphonium Derivative of the Thiolate, $(MeO)_2PO{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}\overset{+}{S}Et{\cdot}CH_2{\cdot}CH_2{\cdot}SEt$. —Thiolate (0·5 g.), 2-bromoethyl ethyl sulphide [8] (0·5 g.; b. p. 69·5—70·5°/10 mm.), and ethanol (2·5 ml.) were kept at 37° for 16 hr. 1 ml. of product was concentrated at <20°/0·5 mm., water (1 ml.) added, and the solution extracted with chloroform (2 × 4 ml.). The aqueous layer (0·37 ml.) was subjected to electrophoresis [2] on a strip (20 × 36 cm.) of Whatman 3 MM paper. The strip between 4 and 16 cm. from the starting line towards the cathode, *i.e.* the section containing positive ions, was soaked for 30 min. in water (30 ml.), the paper removed, and the solution stored at −30°.

Samples were also prepared from thionate and thiolate, alone and mixed, in 0·01N-hydrochloric acid. As in all experiments with thionate, ethanol was added to the dilute acid at the rate of 5 ml. of ethanol/100 ml. of acid. Thionate (about 0·4 mg./ml.) and thionate (about 0·2 mg./ml.) + thiolate (about 0·4 mg./ml.) were kept at 21·8° for 300 min., and thiolate (5 mg./ml. and 10 mg./ml.) at 37° for 200 min. The products were extracted thrice with chloroform, and the aqueous layers stored in the cold. Compounds prepared similarly had been shown to be positively charged.[2]

Hydrolysis Rates of the Unstable Anticholinesterases.—Samples prepared as above were stored at 21·8° or 37°, portions extracted from time to time, and their anticholinesterase activities determined. After 4—5 half-lives a portion was kept at 37° for 1 day, which decomposed the unstable anticholinesterase completely, but only about 5% of the more stable methylsulphonium inhibitor. In preparations from the thiolate alone or from the synthetical method, 5—10% of the initial activity was due to this compound. Other samples contained less than 1%. This residual activity was subtracted from the previous results, which then agreed with those expected for first-order decomposition, with the constants given in Table 1. As one constant depended on two points only no standard error is given for it.

Hydrolyses.—Runs were carried out at 21·80° ± 0·05° or 36·95° ± 0·05°.

For runs with thionate alone, the ester in ethanol was added to the acid to give 5 ml. of ethanol in 100 ml. of acid, and shaken briskly. The thionate concentrations were found by phosphorus analysis. The ionic products were determined at set times by removing samples, extracting them twice with an equal volume of chloroform, estimating phosphorus in the aqueous layer, and multiplying the results by 1·029 to correct for the increase in volume of that layer due to extraction of ethanol from the chloroform, which contained it as a preservative. This factor was obtained by extracting potassium phosphate solutions similarly.

For runs containing thiolate, a solution of the freshly purified compound [2] was heated rapidly to the correct temperature, and a sample withdrawn for analysis. Thionate, when required, was then added in ethanolic solution of known concentration. Runs were then carried out as before.

The anticholinesterase formed was determined on samples after extraction of non-ionic compounds with chloroform. Times were taken from the first moment of shaking with chloroform. Dissolved chloroform was blown out by air, and the determinations carried out immediately, or the samples stored at −30°. They were never left at room temperature for more than 15 min. between extraction and analysis.

The hydrolysis rates of the thiolate at two concentrations in 0·005N-hydrochloric acid at 37° are given by Heath and Vandekar.[2] Those of its sulphoxide and sulphone were determined at the same acid concentration and temperature by the chloroform-extraction method,[9] volume changes being allowed for as described above.

Thiolate from Thionate Solutions.—The concentration of thiolate produced by the end of a run with thionate alone was determined either by the difference between the concentration of ionic products at the end of the run and the initial concentration of thionate, or by the determination of the phosphorus extracted by chloroform. The precision of both methods was only about 5%, in the first because the thiolate concentration was only about 20% of the initial thionate concentration, and in the second because it proved difficult to evaporate the chloroform without losing phosphorus.

[7] Foss, *Acta Chem. Scand.*, 1947, **1**, 8.
[8] Steinkopf, Herold, and Stöhr, *Ber.*, 1920, **53**, 1007.
[9] Heath, *J.*, 1956, 3796.

These methods assume that the only compound extractable by chloroform at the end of a run is thiolate. This was demonstrated in two ways. First, a chloroform extract from the end of a run was concentrated, and subjected to counter-current analysis in a 54-tube stainless steel, Craig [10] machine. One phosphorus band only was found, with partition coefficient between light petroleum (b. p. 100—120°) and water of 1·61, *i.e.*, that of the pure thiolate.[3] Secondly, an aqueous solution was prepared from another extract, kept at 37° for 5 hr., and the phosphorus content and anticholinesterase activity determined. On comparison with the results given in Table 7, the two determinations agreed to within 2% on the assumption that the only phosphorus compound present was the thiolate.

Decomposition of Dry Thiolate.—Thiolate was dried *in vacuo*, and kept at 76° in a stoppered capillary tube. Samples were withdrawn at set times, and the fraction of the phosphorus not extractable by chloroform was determined. The rate of decomposition increased with time, reaching 40% at 16 hr. In the same time 13% of sulphoxide and 1% of sulphone decomposed.

*Rate Equations and Calculations.**—Two reaction schemes which fail are considered first.

(i) $PS \xrightarrow{k_1} PO$, $PS \xrightarrow{k_2} I$, $PO + PS \xrightarrow{k_3} A$, $A \xrightarrow{k_4}$ non-toxic products, where PS = thionate, PO = thiolate, I = ionic phosphates, and A = unstable anticholinesterase.

For runs with thionate alone, this scheme gives $[PO]_\infty$ proportional to $[PS]_0$, not to $[PS]_0^{1\cdot6}$ as is found, and an incorrect dependence of A, the concentration of species A, on time.

(ii) $PS \underset{k_6}{\overset{k_5}{\rightleftharpoons}} X \xrightarrow{k_7} PO$, $PO + PS \xrightarrow{k_3} A$, $A \xrightarrow{k_4}$ non-toxic products, and $PS \xrightarrow{k_7} I$ or $X \xrightarrow{k_7} I$, where k_6 may be 0.

These schemes correspond to the assumption that the intermediate in the isomerisation is an ion pair. They all give $[PO]_\infty$ proportional to $[PS]_0$, which is strong evidence that this hypothesis is incorrect. Calculations also suggest that A is not formed by a direct reaction between PO and PS. Thus, for runs with thionate alone, constants can be chosen which give values of A in good agreement with experiment; but, for mixtures containing thiolate, these constants give values of A 30—50% too low. Thus the rate of formation of A can only depend on [PO][PS] if PS decomposes at a rate far from exponential, which is inconsistent with the rate of formation of ionic phosphates (Table 6), which is roughly exponential, and accounts for most of the decomposition.

The equations for [PS], [X], and [PO] can be obtained from the treatment given by Lowry and John [11] to similar schemes. That for A is:

$$\frac{A(b-a)}{k_5P_0} = \frac{K(k-a)\{\exp(-k_4t) - \exp(-at)\}}{a-k_4} - \frac{K(k-b)\{\exp(-k_4t) - \exp(-bt)\}}{b-k_4}$$
$$- \frac{k_1k_2P_0}{b-a}\left\{\frac{(k-a)\{\exp(-k_4t) - \exp(-2at)\}}{a(2a-k_4)} + \frac{(k-b)\{\exp(-k_4t) - \exp(-2bt)\}}{b(2b-k_4)}\right.$$
$$\left. - \frac{\{(k-a)/b + (k-b)/a\}\{\exp(-k_4t) - \exp(-at-bt)\}}{(a+b-k_4)}\right\}$$

where $P_0 = [PS]_{t=0}$, $Q = [PO]_{t=0}$, and $K = Q + k_1k_2P_0/ab$;

and, for $PS \xrightarrow{k_7} I$, $k = k_2 + k_6$, $k' = k_1 + k_7$, $2a = k + k' - \{(k+k')^2 - 4(kk' - k_1k_6)\}^{\frac{1}{2}}$ and $2b = k + k' + \{(k+k')^2 - 4(kk' - k_1k_6)\}^{\frac{1}{2}}$;

and for $X \xrightarrow{k_7} I$, $k = k_2 + k_6 + k_7$, $2a = k + k_1 - \{(k+k_1)^2 - 4k_1(k-k_6)\}^{\frac{1}{2}}$ and $2b = k + k_1 + \{(k+k_1)^2 - 4k_1(k-k_6)\}^{\frac{1}{2}}$.

(iii) This scheme accounts for the results adequately. In it B = cyclic sulphonium intermediate and C = *OO*-dimethyl phosphorothioate ion, then

$$PS \xrightarrow{k_1} B + C \xrightarrow{k_2} PO,\ B \xrightarrow{k_3} I,\ B + PO \xrightarrow{k_3} A,\ A \xrightarrow{k_4} \text{non-toxic products.}$$

To integrate the equations, it appears to be necessary to put $k_4 = 0$, which will introduce only

* In this section the use of brackets [ ] is restricted to the significance of concentration.

[10] Craig and Post, *Analyt. Chem.*, 1949, **21**, 500.
[11] Lowry and John, *J.*, 1910, 2635.

minor errors, as it is the smallest constant by a factor of about 10. Then, assuming that B is unstable, so that $d[B]/dt = 0$, we obtain:

$$[B] = k_1[PS]/(k_2[C] + k_3)$$

$$[C] = 2\{(1 + bP_0 - b[PS])^{\frac{1}{2}} - 1\}/b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where $b = 2k_2/k_3$;

$$[PO] = P_0 - [PS] - [C] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

$$k_3bA/2k_5 = (1/b + Q)\{(a - bx)^{\frac{1}{2}} - 1\} - (P_0 - x) + \{(a - bx)^{3/2} - 1\}/3b \quad . \quad (3)$$

in which $x = [PS] = P_0 \exp(-k_1t)$, and $a = (1 + bP_0)$. The final equations were obtained by dividing equations of the type: dy/dt by $d[PS]/dt$, and integrating the resulting equations with respect to [PS].

The theoretical curve in the Figure was obtained by putting [PS] = 0 in eqn. (1) and plotting the calculated values over the experimental range.

The constants given in Table 8 for the thiolate–thionate reactions at 37° were calculated as follows from the results summarised here. $P_0 = 1{\cdot}07 \times 10^{-3}$M, $Q = 1{\cdot}48 \times 10^{-3}$M, and $C_\infty = 8{\cdot}7 \times 10^{-4}$M, whence $b = 1{\cdot}035 \times 10^3$ mole^{-1} from eqn. 1. At $t = 7{\cdot}0$, 8·5, and 9·5 min., respectively, $C = 3{\cdot}96 \times 10^{-4}$M, $4{\cdot}22 \times 10^{-4}$M, and $5{\cdot}00 \times 10^{-4}$M. The best value of k_1, 0·075 min.$^{-1}$, obtained by putting these values into eqn. 1, gives [C] = $3{\cdot}96 \times 10^{-4}$M, $4{\cdot}52 \times 10^{-4}$M, and $4{\cdot}83 \times 10^{-4}$M. At the same times, A = 1780, 1970, and 2030 units, whence, from eqn. 3, $k_5/k_3 = 1{\cdot}31 \times 10^7$, $1{\cdot}27 \times 10^7$, and $1{\cdot}22 \times 10^7$ (average, $1{\cdot}27 \times 10^7$) in terms of units of A, and moles of the other reagents.

If dimethyl phosphorothioate ions are added, there is an additional constant concentration, C_0, of C present throughout the reaction. Then, for the additional amount of C produced by decomposition of the thionate, $[C] = 2\{(d^2 + bP_0 - b[PS])^{\frac{1}{2}} - d\}/b$, where $d = 1 + bC_0/2$. At $t = \infty$, [PS] = 0, and $[PO]_\infty = P_0 - [C]$. In an experiment carried out at 21·8°, $C_0 = 6{\cdot}93 \times 10^{-3}$M, and $P_0 = 1{\cdot}32 \times 10^{-3}$M, whence, the constants in Table 8 being used, $[PO]_\infty = 0{\cdot}822P_0$.

For runs with thiolate alone, the only additional reaction to be considered is: PO $\xrightarrow{k_6}$ B + C, the reverse of one already given. Then: $d[B]/dt = k_6[PO] - k_5[B][PO] - k_3[B] = 0$. If $k_5[B][PO]$ is small compared to the other two terms, $[B] = k_6[PO]/k_3$. As the constants are all great compared with k_6 $dA/dt = k_5[B][PO] - k_4A = 0$, whence $k_6 = k_3k_4A/k_5[PO]^2$. From Table 7, $A/[PO]^2 = 240$; k_4 and k_3/k_5 are given in Table 8; whence $k_6 = 3{\cdot}05 \times 10^{-5}$ min.$^{-1}$.

The Activity of the Unstable Anticholinesterase.—A direct determination was carried out on the solution obtained by the electrophoresis of the synthetic sample. The solution, $1{\cdot}2 \times 10^{-4}$M in phosphorus, contained 12,000 units of anticholinesterase activity, of which 950 units were of the methylsulphonium derivative of the thiolate. This [2] has $I_{50} = 3{\cdot}9 \times 10^{-6}$M, whence its concentration was $0{\cdot}37 \times 10^{-4}$M. Hence the I_{50} of the substance A is given by $(1{\cdot}20 - 0{\cdot}37) \times 10^{-4}$M/(12,000 − 950), *i.e.* $6{\cdot}9 \times 10^{-6}$M.

This value may be very high. Only about 25% of the anticholinesterase activity placed on the strip was recovered although none was found elsewhere. Perhaps the anticholinesterase was not removed completely from the strip, but, as the strip became warm during electrophoresis, which lasted 2 hr., it is equally likely that the anticholinesterase was decomposed, probably after it had moved towards the cathode. The value is inconsistent with other results, as shown below.

The I_{50} value can be calculated from the rate constants for the production of ions of all kinds from the thiolate alone at two concentrations (already reported [2]). The constants are: $4{\cdot}50 \times 10^{-5}$ min.$^{-1}$ at 0·94 mg./ml., and $5{\cdot}77 \times 10^{-5}$ min.$^{-1}$ at 4·70 mg./ml. The difference being assumed to be due solely to second-order reactions producting anticholinesterases, at infinite dilution $k = 4{\cdot}18 \times 10^{-5}$ min.$^{-1}$, so that, at the higher concentration, the second-order reactions contribute $1{\cdot}59 \times 10^{-5}$ min.$^{-1}$. The concentrations of methylsulphonium compound found [2] require a constant of $1{\cdot}33 \times 10^{-5}$ min.$^{-1}$, leaving $0{\cdot}26 \times 10^{-5}$ min.$^{-1}$ for the rate of formation of the unstable anticholinesterase. This is equal to the rate of decomposition, *i.e.* to k_4A. When the concentration of PO is 4·70 mg./ml., A, in the usual units, is 5,300 (calculated from Table 7). Then $0{\cdot}26 \times 10^{-5} = k_4AI_{50}/[PO]$, whence $I_{50} = 1{\cdot}4 \times 10^{-6}$M.

By similar reasoning, it can be shown that, if the I_{50} is $6{\cdot}9 \times 10^{-6}$M, the difference between the rate constants at the two concentrations would be $2{\cdot}61 \times 10^{-5}$ and not $1{\cdot}59 \times 10^{-5}$ min.$^{-1}$,

as observed. This discrepancy appears too great to be accounted for by either experimental error or concentration effects.

If, in reactions of thiolate alone, k_5[B][PO] is not negligible, $k_6 = (k_4A[PO] + k_3/k_5)/[PO]^2$. For $I_{50} = 6{\cdot}9 \times 10^{-6}$M, $k_3/k_5 = 11{\cdot}4$ mg./ml., not much above the higher concentrations of the thiolate. Then A is not proportional to [PO]^2. For $I_{50} = 1{\cdot}4 \times 10^{-6}$M, $k_3/k_5 = 56{\cdot}2$ mg./ml., which is large compared with the concentration of PO, so that the original formula is a good approximation.

I thank Dr. G. Schrader and his colleagues for the phosphorus compounds, Dr. G. S. Hartley for the ethyl hydroxyethyl sulphide, Dr. H. A. Krebs and Dr. D. E. Hughes for the Craig counter-current separator, Dr. D. F. Elliott for a 50-tube separator of the type designed by Lathe and Ruthven [12] used in some trial experiments, and Mr. D. E. A. Groom for technical assistance.

MEDICAL RESEARCH COUNCIL LABORATORIES,
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[12] Lathe and Ruthven, *Biochem. J.*, 1951, **49**, 540.

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328. *The Preparation of 7- and 9-Glucopyranosyl and -Xylopyranosyl Derivatives of 8-Azaxanthine (5 : 7-Dihydroxy-v-triazolo[d]pyrimidine).*

By J. BADDILEY, J. G. BUCHANAN, and G. O. OSBORNE.

N-Glycosyl derivatives of 8-azaxanthine and of triazoles have been prepared in the course of a study on purine antimetabolites.

Acetylglycosyl azides with dimethyl acetylenedicarboxylate readily give *N*-glycosyltriazoles (I; R = *O*-acetylglycosyl). These with ammonia yield the dicarboxyamides (II; R = glycosyl), which with hypobromite are converted into mixtures containing both 7- and 9-glycosyl derivatives of 8-azaxanthine (V and VI; R = glycosyl). The separation and orientation of these *N*-glycosyl derivatives has been achieved.

INTERESTING medical and biological properties are displayed by certain analogues of the naturally occurring purine bases. Under the stimulus of the antibacterial and carcinostatic behaviour encountered in this field, many such analogues have been prepared.[1] Purine bases, bearing a wide variety of functional groups, represent the bulk of compounds studied in this work, although recently more attention has been given to modification of the purine ring system itself. In the latter class the *v*-triazolo[*d*]-pyrimidines (8-azapurines) have been much studied, 5-amino-7-hydroxy-*v*-triazolo[*d*]-pyrimidine (8-azaguanine) being regarded as particularly promising from a chemotherapeutic point of view. The search for purine antagonists has mainly involved free bases. Since some of these are converted into nucleosides and nucleotides in bacteria and other living systems, it is clear that *N*-glycosyl derivatives of the appropriate bases also possess potential antimetabolite function. However, relatively few compounds of this sort are available for testing. For instance, the literature contains no chemical synthesis of an 8-azapurine nucleoside.* The present work arose from our studies on glycosyl azides, and particularly β-D-ribofuranosyl azide, as intermediates for the chemical synthesis of certain purine nucleotide precursors.[2,3] We wished to compare the behaviour of the sugar azides with that of alkyl and aryl azides towards unsaturated compounds. This has now led to syntheses of both the 7- and the 9-glycosyl derivative of 8-azaxanthine.

* Ribofuranosyl derivatives of 8-aza-adenine and 8-azahypoxanthine have been prepared by Davoll, (cf. Matthews, Ciba Foundation Symposium, "Chemistry and Biology of Purines," London, 1957, p. 270) but the method of synthesis has not yet been disclosed.

[1] Hitchings and Elion, 3rd Internat. Congr. Biochemistry, Brussels, 1955, p. 55.
[2] Baddiley, Buchanan, Handschumacher, and Prescott, *J.*, 1956, 2818.
[3] Baddiley, Buchanan, Hodges, and Prescott, *J.*, 1957, 4767.

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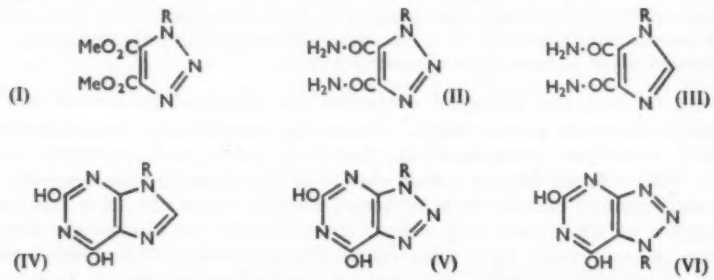
Xylopyranosyl and glucopyranosyl derivatives have been prepared in the first instance, although there are indications that the synthesis may be extended to ribofuranosyl derivatives.

Curtius and Raschig [4] have described the preparation of dimethyl 1-benzyl-1 : 2 : 3-triazole-4 : 5-dicarboxylate (I; R = CH_2·Ph) from benzyl azide and dimethyl acetylenedicarboxylate. In the present work an analogous reaction was used. Dimethyl 1-(2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1 : 2 : 3-triazole-4 : 5-dicarboxylate (I; R = tetra-*O*-acetyl-β-D-glucopyranosyl) was obtained in excellent yield by heating dimethyl acetylenedicarboxylate (1 or 2 mols.) with 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucopyranosyl azide in benzene or acetone for several hours. Dimethyl 1-(2 : 3 : 4-tri-*O*-acetyl-β-D-xylopyranosyl)-1 : 2 : 3-triazole-4 : 5-dicarboxylate (I; R = tri-*O*-acetyl-β-D-xylopyranosyl) was obtained similarly. The acetylated glycosyltriazoles with methanolic ammonia at 0° overnight gave 1-β-D-glucopyranosyl- and 1-β-D-xylopyranosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide (II; R = β-D-glycopyranosyl).

The identity of these amides was confirmed when N-hydrochloric acid at 100° liberated the parent sugar (detected by paper chromatography) and a base, which was isolated and identified as 1 : 2 : 3-triazole-4 : 5-dicarboxyamide by conversion, *via* a presumed monoamide intermediate, into the dicarboxylic acid.

The preparation of xanthosine (IV; R = β-D-ribofuranosyl) and of 9-xylosylxanthine by the action of hypobromite on the corresponding glycosylglyoxaline-4 : 5-dicarboxyamides (III; R = glycosyl) has been reported by Spring and his collaborators.[5,6] In the same way, but under somewhat different reaction conditions, 1-xylosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide yielded cyclic products. After treatment with an excess of aqueous potassium hypobromite at 2° for 18 hr., then at 60° for 30 min., paper chromatograms revealed a major product which appeared in ultraviolet light as a bright blue, fluorescent spot, still visible after exposure to hydrochloric acid vapour. The reaction mixture was

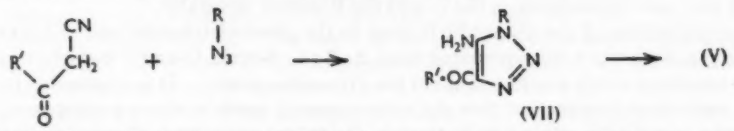


then diluted and percolated through a column of Dowex-2 resin in the formate form; elution with 0·1M- or 0·2M-ammonium formate removed two major components. The first of these (A) showed maximum ultraviolet absorption at 278 mμ in neutral, aqueous solution. The second (B) exhibited maxima at 250 and at 278 mμ. These fractions were concentrated and ammonium formate was sublimed from the solid residues; materials A and B remained as pale powders.

Acid hydrolysis of both A and B gave xylose and 8-azaxanthine (V; R = H) (detected on paper chromatograms). A and B had similar R_F values in the solvent systems used, but the resulting spots exhibited marked differences in fluorescent behaviour. Whereas A was detected in ultraviolet light as a bright blue fluorescence where basic solvent systems were used or after exposure of chromatograms to ammonia, B gave a similar blue fluorescence only under acid conditions.

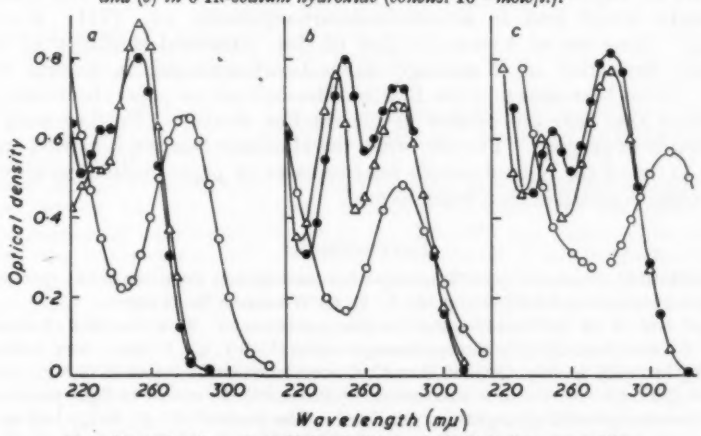
[4] Curtius and Raschig, *J. prakt. Chem.*, 1930, **125**, 466.
[5] Baxter and Spring, *J.*, 1947, 378.
[6] Howard, McLean, Newbold, Spring, and Todd, *J.*, 1949, 232.

Although Spring's work on the corresponding glyoxaline derivatives led to the isolation of only one isomer, 9-xylosylxanthine,[5] the presence of A and B above pointed to the formation of both 7- and 9-xylosyl-8-azaxanthine (VI and V; R = xylosyl) in the present case. Since the spectroscopic differences between A and B were considerable, comparison with the appropriate methylated bases appeared promising as a means of orientation. Since the Hofmann reaction can yield only 7- and 9-isomers in this case, only one reference compound, either 7- or 9-methyl-8-azaxanthine, was required. 9-Methyl-8-azaxanthine (V; R = Me) was synthesised: methyl azide and cyanoacetamide gave the aminotriazolecarboxyamide (VII; R = Me, R′ = NH_2) which was converted into the azaxanthine derivative (V; R = Me) by fusion with urea at 170—180°.



Dimroth [7,8] synthesised several derivatives of 1-phenyl-1 : 2 : 3-triazole by reaction between phenyl azide and malonic or cyanoacetic esters. He proved that phenyl azide and methyl cyanoacetate yield exclusively the 1-phenyl isomer (VII; R = Me, R′ = OMe). Recently Hoover and Day [9] prepared triazole derivatives (VII; R = CH_2Ph, R′ = OMe or NH_2) from benzyl azide and malonic or cyanoacetic ester. It has been assumed by the American authors that phenyl and benzyl azide would react similarly, to give triazoles with identical orientation of substituents. In our synthesis of 9-methyl-8-azaxanthine as outlined above we have also made the reasonable assumption that phenyl azide and methyl azide would react similarly. We feel, however, that the analogy between phenyl azide and methyl or benzyl azide is not rigid and a more rigorous proof of the orientation of substituents in the *N*-methyltriazole (VII; R = Me, R′ = NH_2) is under investigation.

Absorption spectra of N-*xylosyl-8-azaxanthine and of* 9-*methyl-8-azaxanthine* (*a*) *at* pH 2·2, (*b*) *at* pH 7·0, *and* (*c*) *in* 0·1N-*sodium hydroxide* (*concns.* 10^{-4} *mole/l.*).



○ 7-*Xylosyl-* (*A*). ● 9-*Xylosyl-* (*B*). △ 9-*Methyl-8-azaxanthine.*

9-Methyl-8-azaxanthine (V; R = Me) and material B are very similar spectroscopically (see Figure). At pH 7 both displayed two peaks (maxima at 245 and 278 mμ, and 250

[7] Dimroth, *Ber.*, 1902, **35**, 4041.
[8] Dimroth, *Annalen*, 1909, **364**, 183.
[9] Hoover and Day, *J. Amer. Chem. Soc.*, 1956, **78**, 5832.

and 278 mμ, respectively), compared with a single peak (278 mμ) in the case of material A. At pH 2·2 both compounds gave a single peak (255 mμ) with a shoulder whereas the position of the peak of A remained unchanged (278 mμ). In 0·1N-sodium hydroxide solution, however, the maximum of A moved to 310 mμ, whereas the maxima of 9-methyl-8-azaxanthine and B were substantially those recorded at pH 7. On this evidence, material A was formulated as the 7-xylosyl (VI) and B as the 9-xylosyl derivative (V). The fluorescence properties of B resemble those of 9-methyl-8-azaxanthine, in accordance with this formulation.

From 1-D-glucopyranosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide (III; R = glucosyl), glucopyranosyl derivatives similar to A and B in absorption and fluorescence were obtained and were formulated as the 7- and the 9-isomer, severally.

The configuration of the glycosidic linkage in the glucosyl-triazoles and -8-azaxanthines is certainly β, since they were prepared from 2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucopyranosyl azide by reactions which would not affect the glycosidic centre. It is reasonable to assume from its method of preparation that the xylopyranosyl azide is also a β-compound, and so the triazoles and 8-azaxanthine derivatives in the xylose series are β-glycosyl derivatives.

In a recent publication,[10] Smith and Matthews describe the isolation of a ribosyl-8-azaxanthine from *Bacillus cereus* grown in a medium containing 8-azaxanthine. The ultraviolet absorption maximum (257 mμ in 0·1N-hydrochloric acid) recorded by them closely resembles that of 9-methyl-8-azaxanthine and of B, and is thus consistent with the ribosyl derivative's being a 9-isomer.

It would be expected that the the Hofmann reaction on the *N*-glycosyltriazoledicarboxyamides would lead to aminotriazolecarboxyamides, *e.g.*, (VII; R = glycosyl, R′ = NH_2). These are of interest in view of their structural similarity to the ribose 5-phosphate derivative of 5-aminoglyoxaline-4-carboxyamide, a natural nucleotide precursor. It has been shown by the Bratton–Marshall test on paper chromatograms that compounds of this type are present in the reaction mixture. Further work on their identification is in progress. Further, when the Hofmann reaction is carried out at 2° it is possible to detect the *N*-bromoamide intermediates by paper chromatography, little or no azaxanthine derivatives then being formed.

Experimental

Unless indicated otherwise, ascending paper chromatograms were run in the system, propan-1-ol–aqueous ammonia (*d* 0·880)–water (6 : 3 : 1), on Whatman No. 4 paper.

Dimethyl 1-(2 : 3 : 4 : 6-*Tetra*-O-*acetyl*-β-D-*glucopyranosyl*)-1 : 2 : 3-*triazole*-4 : 5-*dicarboxylate*.—2 : 3 : 4 : 6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide[11] (3·7 g., 1 mol.) was heated under reflux for 2½ hr. with freshly distilled dimethyl acetylenedicarboxylate[12] (1·8 g., 1·2 mol.) in dry benzene (30 c.c.). The yellow solution was poured into an excess of light petroleum (b. p. 40—60°); the precipitated oil rapidly crystallised. The *product* (4·7 g., 96%) had m. p. 153°, after recrystallisation from ethanol (Found: C, 46·6; H, 4·9; N, 7·8. $C_{20}H_{25}O_{13}N_3$ requires C, 46·9; H, 4·9; N, 8·1%). The yield was 85% when acetone was the solvent. When 2 mols. of the acetylene were used, reaction in benzene gave a 90% yield of the above product.

1-β-D-*Glucopyranosyl*-1 : 2 : 3-*triazole*-4 : 5-*dicarboxyamide*.—Dimethyl 1-(2 : 3 : 4 : 6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1 : 2 : 3-triazole-4 : 5-dicarboxylate (1·05 g.) was treated at 0° overnight with dry methanol (30 c.c.) saturated with ammonia. Evaporation of solvent to small volume, followed by the addition of ether, precipitated a white gum which hardened rapidly (0·54 g., 85%). Recrystallised from aqueous methanol the *diamide* formed colourless crystals of indeterminate m. p. (Found, in sample dried at 50°/1 mm. for 12 hr.: C, 36·8; H, 5·1; N, 21·4. $C_{10}H_{15}O_7N_5,\frac{1}{2}H_2O$ requires C, 36·8; H, 4·9; N, 21·5%).

Dimethyl 1-(2 : 3 : 4-*Tri*-O-*acetyl*-β-D-*xylopyranosyl*)-1 : 2 : 3-*triazole*-4 : 5-*dicarboxylate*.—2 : 3 : 4-Tri-*O*-acetyl-β-D-xylopyranosyl azide (3·0 g., 1 mol.) was heated under reflux for 5 hr. with dimethyl acetylenedicarboxylate (2·3 g., 1·55 mol.) in dry benzene (30 c.c.), then poured

[10] Smith and Matthews, *Biochem. J.*, 1957, **66**, 323.
[11] Bertho, *Ber.*, 1930, **63**, 836.
[12] Huntress, Lesslie, and Bornstein, *Org. Synth.*, 1952, **32**, 55.

into an excess of light petroleum (b. p. 40—60°). The precipitated oil crystallised on trituration with methanol. The colourless *ester* (3·4 g., 76%) had m. p. 114° after recrystallisation from ethanol (Found: C, 46·5; H, 4·8; N, 10·0. $C_{17}H_{21}O_{11}N_3$ requires C, 46·1; H, 4·7; N, 9·5%).

1-β-D-*Xylopyranosyl*-1 : 2 : 3-*triazole*-4 : 5-*dicarboxyamide*.—Dimethyl 1-(2 : 3 : 4-tri-*O*-acetyl-β-D-xylopyranosyl)-1 : 2 : 3-triazole-4 : 5-dicarboxylate (2·5 g.) was treated at 0° overnight with dry methanol (30 c.c.) saturated with ammonia. Concentration of the solution *in vacuo* led to the separation of colourless crystals (1·3 g., 88%). Addition of ether to the mother liquors gave a further small crop (0·05 g.). The *diamide* was purified by recrystallisation from aqueous methanol (Found, in sample dried at 50°/1 mm. for 12 hr.: C, 36·7; H, 5·1; N, 23·7. $C_9H_{13}O_6N_5,\frac{1}{2}H_2O$ requires C, 36·5; H, 4·7; N, 23·7%).

Acid Hydrolysis of Triazole Derivatives.—(*a*) 1-Glucosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide (69 mg.) in N-hydrochloric acid (5 ml.) was kept at 90° for 1 hr. The solid (18 mg.) which separated was filtered off. Treatment of this product with N-sodium hydroxide at 100° for 2 hr., followed by dilution of the resulting solution, passage down a Dowex-50 column (H^+ form), and concentration of the effluent, gave a white solid (5 mg.). This had m. p. 198°, alone or in admixture with 1 : 2 : 3-triazole-4 : 5-dicarboxylic acid prepared from 1-benzyl-1 : 2 : 3-triazole-4 : 5-dicarboxylic acid [14] by debenzylation. (*b*) Milligram quantities of 1-glucosyl- and 1-xylosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide in N-hydrochloric acid (0·2 ml.) were kept at room temperature for 20 min., then at 95°. Paper chromatography revealed considerable hydrolysis of the xylosyl derivative at room temperature. The glucosyl derivative appeared to be unaffected. Both xylosyl and glucosyl derivative were completely hydrolysed after 20 min. at 95°. Initial decomposition products were the parent sugars (detected by aniline phthalate spray) and a base, presumably 1 : 2 : 3-triazole-4 : 5-dicarboxyamide.

	R_F
1-Glucosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide	0·63
1-Xylosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide	0·66
1 : 2 : 3-Triazole-4 : 5-dicarboxyamide (by hydrolysis)	0·59

Further acid hydrolysis of 1 : 2 : 3-triazole-4 : 5-dicarboxyamide led to the appearance of a component with R_F 0·27, probably a monamide, and finally to 1 : 2 : 3-triazole-4 : 5-dicarboxylic acid, R_F 0·18.

All these substances were readily detected on paper chromatograms as opaque spots in ultraviolet light of 254 mμ wavelength. It should be noted that the actual ultraviolet absorption maxima of these compounds lie in the 220—230 mμ region. The two glycosyl derivatives slowly developed rather weak blue colours with the periodate–Schiff spray.

Action of Hypobromite on 1-β-D-*Xylopranosyl*-1 : 2 : 3-*triazole*-4 : 5-*dicarboxyamide*.—Freshly prepared potassium hypobromite [5] (15 ml.) at 2° was added to 1-xylopyranosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide (740 mg.), the mixture being maintained for 18 hr. at this temperature, then for 30 min. at 65°. After dilution with water (50 ml.) the solution was passed down a column of Dowex-2 (formate) (15 × 3 cm.; 200—400 mesh). The resin was washed with water and products were eluted with 0·1M-ammonium formate solution at pH 7 (fractions 1—180) and then with 0·2M-ammonium formate. Fractions 230—296 (each of 10 ml.) contained the component A; fractions 342—451 contained the component B.

7-β-D-*Xylopranosyl*-8-*azaxanthine*. The combined fractions 230—296 were evaporated to dryness at 35° (rotatory evaporator) and ammonium formate was removed by sublimation *in vacuo* at 60°. The residual white powder was recrystallised from water. The *N-glycosyl derivative* (59 mg.) was dried for 8 hr. at 85°/1 mm. (Found: C, 38·2; H, 4·3; N, 25·0. $C_9H_{11}O_6N_5$ requires C, 37·9; H, 3·9; N, 25·1%). The total 7-xylosyl derivative content of fractions 230—296, estimated spectrophotometrically, was 110 mg.

9-β-D-*Xylopyranosyl*-8-*azaxanthine*. Fractions 342—381 (which were halide-free) and fractions 382—451 (which contained a little ammonium bromide) were evaporated as two batches as before. Ammonium formate was removed by sublimation and the residual materials were dissolved in wet methanol and reprecipitated by ether. The hygroscopic, freshly precipitated 9-*xylosyl derivative* (15 mg.) from fractions 342—381 was dried at 60°/1 mm. for 12 hr. (Found: C, 33·2; H, 5·3; N, 20·9. $C_9H_{11}O_6N_5,2\frac{1}{2}H_2O$ requires C, 32·8; H, 5·3; N, 20·6%). The material from fractions 382—451 was difficult to purify. Ammonium bromide

[13] Bertho, *Annalen*, 1949, **562**, 229.
[14] Wiley, Hussing, and Moffatt, *J. Org. Chem.*, 1956, **21**, 190.

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was finally removed by adsorption of the xylosyl derivative on charcoal, followed by elution with ethanol–ammonia–water, but losses were considerable. The 9-xylosyl derivative content of fractions 342—451, estimated spectrophotometrically, was 90 mg.

Action of Hypobromite on 1-β-D-*Glucopyranosyl*-1 : 2 : 3-*triazole*-4 : 5-*dicarboxyamide.*—Freshly prepared potassium hypobromite [5] (15 ml.) at 2° was added to 1-glucosyl-1 : 2 : 3-triazole-4 : 5-dicarboxyamide (750 mg.). After 18 hr. at this temperature the mixture was maintained at 65° for 30 min., diluted with water (50 ml.), and percolated through a Dowex-2 resin column in the formate form (200—400 mesh; 15 × 3 cm.). The resin was washed with water and with 0·1M-ammonium formate (1 l.) (pH 7), and the products were eluted with 0·2M-ammonium formate at pH 7, 10 ml. fractions being collected. Tubes 44—74 which exhibited a single absorption maximum at 278 mμ were combined. Tubes 141—200 which exhibited maxima at 250 and 278 mμ were also combined.

7-β-D-*Glucopyranosyl*-8-*azaxanthine.* The combined fractions 44—74 were evaporated to dryness at 35° (rotary evaporator) and ammonium formate was removed by sublimation *in vacuo* at 60°. The residual white powder (150 mg.) was recrystallised from water. The *N-glycosyl derivative* was dried for 12 hr. at 60°/1 mm. (Found: C, 36·9; H, 4·7; N, 21·7. $C_{10}H_{13}O_7N_5,\frac{1}{2}H_2O$ requires C, 37·1; H, 4·4; N, 21·6%).

9-β-D-*Glucopyranosyl*-8-*azaxanthine.* Combined fractions 141—200 were evaporated and ammonium formate was removed as before. The residue was dissolved in methanol and reprecipitated by the addition of ether. The material obtained in this way (68 mg.) contained a little inorganic halide. It was dissolved in a small volume of aqueous methanol and reprecipitated by the addition of ethanol. The *glycosyl derivative* was dried for 12 hr. at 80°/1 mm. (Found: C, 32·6; H, 4·8. $C_{10}H_{13}O_7N_5,3H_2O$ requires C, 32·8; H, 5·2%).

Hydrolysis of N-*Glycosyl*-8-*azaxanthines.*—N-Hydrochloric acid (0·2 ml.) was added to milligram quantities of the four glycosyl derivatives. Paper chromatograms revealed no decomposition after 30 min. at room temperature. After 1 hr. at 95° both 7-glycosyl

	R_F	Conditions for fluorescence
7-Glucopyranosyl-8-azaxanthine	0·38	Basic
9-Glycopyranosyl-8-azaxanthine	0·38	Acidic
7-Xylopyranosyl-8-azaxanthine	0·42	Basic
9-Xylopyranosyl-8-azaxanthine	0·41	Acidic
8-Azaxanthine	0·32	Acidic

derivatives were completely hydrolysed to the parent sugars (detected by benzidine spray [18]) and 8-azaxanthine. The 9-xylosyl derivative was also completely hydrolysed under these conditions, but hydrolysis of the 9-glucosyl derivative was not quite complete. After 2 hr. at 95° the 9-glucosyl derivative was completely hydrolysed.

Detection of these compounds by their fluorescence appears preferable to detection by their opacity under non-fluorescent conditions.

5-*Amino*-1-*methyl*-1 : 2 : 3-*triazole*-4-*carboxyamide.*—Cyanoacetamide (3·7 g., 1·0 mol.) and methyl azide (6·0 g., 2·4 mol.) were added to a stirred, freshly prepared solution from sodium (1 g.) in ethanol (100 ml.), and the mixture was then heated under reflux for 1 hr. After cooling, the crystalline product (1·45 g.) was filtered off and washed with cold water and cold ethanol. Recrystallised from ethanol the *triazole* formed white needles, m. p. 248° (Found: C, 33·9; H, 5·0. $C_4H_7ON_5$ requires C, 34·0; H, 5·0%).

The compound ran as a single spot, R_T 0·73, detected by ultraviolet absorption and by the purple colour produced with a modified Bratton–Marshall spray reagent.[16] When an ethanol solution of 5-amino-1-methyl-1 : 2 : 3-triazole-4-carboxyamide was saturated with hydrogen chloride the base hydrochloride separated readily.

9-*Methyl*-8-*azaxanthine.*—Finely powdered urea (500 mg.) was fused with 5-amino-1-methyl-1 : 2 : 3-triazole-4-carboxyamide hydrochloride (500 mg.) at 170—180° for 2½ hr. The product was dissolved in a little hot water and the solution diluted and passed down a Dowex-50 resin column (H^+ form). The effluent and washings were combined, adjusted to pH 10 (ammonium hydroxide), and percolated through a Dowex-2 resin column (10 × 1·5 cm.; formate form) which was then washed with water and eluted with 0·1N-formic acid (150 ml.). The eluate was evaporated to dryness at 35° (rotary evaporator) and the residual white solid recrystallised

[18] Horrocks, *Nature*, 1949, **164**, 444.
[16] Greenberg and Spilman, *J. Biol. Chem.*, 1956, **219**, 411.

from water. 9-*Methyl*-8-*azaxanthine* (63 mg.) formed white needles, m. p. 320° (decomp.) (Found: C, 35·9; H, 3·4; N, 41·9. $C_5H_5O_2N_5$ requires C, 36·1; H, 3·0; N, 41·7%). It was homogeneous (R_F 0·68) when examined by paper chromatography. The compound was detected on the paper by its brilliant blue fluorescence after exposure to hydrochloric acid vapour.

This work was supported by a grant from the British Empire Cancer Campaign.

KING'S COLLEGE, UNIVERSITY OF DURHAM,
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329. *Steroids and Walden Inversion. Part XXXIX.* The Halogenation of 5α-Cholestan-6-one and the Pyrolysis of 5-Chloro-5α-cholestan-6-one.*

By C. W. SHOPPEE, R. H. JENKINS, and G. H. R. SUMMERS.

5-Chloro-5α-cholestan-6-one, prepared from 5-hydroxy-5α-cholestan-6-one and hydrogen chloride, has also been obtained from 5 : 6β-epoxy-5β-cholestane by a configurationally unambiguous method; on pyrolysis at 290°/15 mm. it yields hydrogen chloride (1 mol.) and 5α-cholestan-6-one (~0·5 mol.), with an unidentified compound which appears to contain two steroid nuclei. 5α-Cholestan-6-one by monobromination, and 5-hydroxy-5α-cholestan-6-one by treatment with hydrogen bromide, give a mixture of 5α-bromo-, 7α-bromo-, and 7 : 7-dibromo-5α-cholestan-6-one. 5α-Cholestan-6-one by dibromination in the presence of hydrogen bromide is converted into 5α : 7α-dibromo-5α-cholestan-6-one, which is transformed into 5α : 7β-dibromo-5α-cholestan-6-one.

SOME years ago Dr. H. Grasshof, of Eschwege, West Germany, directed the attention of one of us to some unfinished and unpublished work described in his Inaugural Dissertation.[1] Grasshof converted cholest-5-ene (I) by perbenzoic acid into 5 : 6α-epoxy-5α-cholestane (II), which by acetolysis with potassium acetate in acetic anhydride at ~140° gave 5α-cholestane-5 : 6β-diol 6-acetate [2] (III; R = Ac), m. p. 109°, $[\alpha]_D$ −47° (*c* 1·2 in C_6H_6), hydrolysed by methanolic potassium hydroxide to 5α-cholestane-5α : 6β-diol [2,3,4,5] (III; R = H). Oxidation with chromium trioxide–acetic acid at 15° furnished 5-hydroxy-5α-cholestan-6-one, m. p. 149°, $[\alpha]_D$ −56° (*c* 0·8 in C_6H_6) [3,4,5] (IV), which proved unexpectedly resistant to dehydration; distillation at 300°/15 mm. or heating with acetic anhydride at 165° was without effect, whilst treatment with hydrogen chloride in chloroform at 15° gave a chloro-ketone, m. p. 115°, $[\alpha]_D$ −122° (*c* 0·85 in C_6H_6). Grasshof regarded this as either 5-chloro-5α-cholestan-6-one (VII) or 4ξ-chloro-5α-cholestan-6-one (VIII) formed by dehydration of (IV) to cholest-4-en-6-one and Markovnikov addition of hydrogen chloride thereto. We have prepared 4β-chloro-5α-cholestan-6-one (VIII), m. p. 174°, by addition of hydrogen chloride to cholest-4-en-6-one in chloroform; it is different from Grasshof's chloro-ketone, and we now show that the chloro-ketone is (VII).

Cholest-5-ene (I) with perbenzoic acid furnished 5 : 6β-epoxy-5β-cholestane [3] (V), converted by hydrogen chloride in chloroform at 15° with diaxial fission and inversion of configuration at $C_{(5)}$ into 5-chloro-5α-cholestan-6β-ol (VI). This was oxidised by chromium trioxide–acetic acid at 15° to 5-chloro-5α-cholestan-6-one (VII), m. p. 115°, $[\alpha]_D$ −120°, identical with Grasshof's compound. Reduction of the chloro-ketone with lithium aluminium hydride in ether at 36°, or with sodium borohydride, gave a gelatinous product and a

* Part XXXVIII, *J.*, 1957, **4364**. The paper by Evans and Summers, *J.*, 1957, 906, may be considered a part of this Series.

[1] H. Grasshof, Inaug.-Diss., Göttingen, 1935.
[2] Heilbron, Shaw, and Spring, *Rec. Trav. chim.*, 1938, **57**, 529.
[3] Ruzicka, Furter, and Thomann, *Helv. Chim. Acta*, 1933, **11**, 332.
[4] Reich, Walker, and Collins, *J. Org. Chem.*, 1951, **16**, 1753.
[5] D. N. Jones, Lewis, Shoppee, and Summers, *J.*, 1955, 2876.

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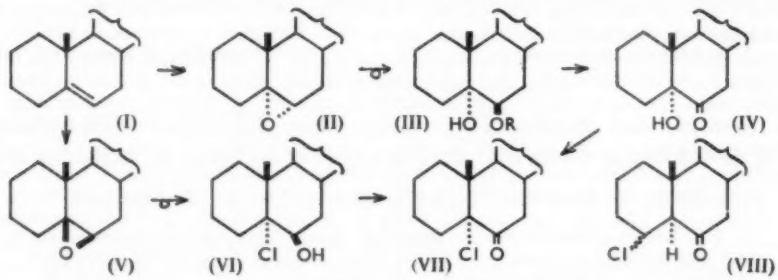
satisfactory chromatographic separation of the 6-epimeric chlorohydrins could not be achieved; reduction with zinc and acetic acid gave 5α-cholestan-6-one [5,6] (X), m. p. 98°, $[\alpha]_D$ −7°.

The axial 5α-chloro-structure of the chloro-ketone (VII) is confirmed by comparison of its ultraviolet and infrared absorption spectra with those of 5α-cholestan-6-one (X) and



its substitution products. The displacement of the absorption maximum toward longer wavelengths by 18 mμ, and the change in intensity (cf. Table 1, where data are for EtOH solutions), correspond well with the average values found for α-bromo-ketones (axial, $\Delta\lambda_{max.}$ +28 mμ, Δ log ε 0·6; equatorial, $\Delta\lambda_{max.}$ −5 mμ, Δ log ε 0) and for a chloro-ketones (axial, $\Delta\lambda_{max.}$ +15 mμ, Δ log ε 0·4; equatorial, $\Delta\lambda_{max.}$ −7 mμ, Δ log ε 0·2) found by Cookson.[7] The displacements of the absorption maxima and the changes in intensity found for 5-bromo-5α-cholestan-6-one (XIII) and for 5-hydroxy-5α-cholestan-6-one (IV) likewise correspond with Cookson's observations [7] in the 3β-acetoxy-5α-cholestan-6-one series.

TABLE 1.

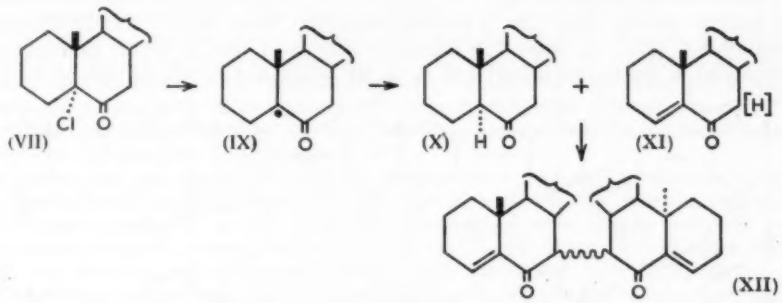
	$\lambda_{max.}$	$\Delta\lambda_{max.}$	log ε	Δ log ε
5α-Cholestan-6-one (X)	284	—	1·6	—
5-Chloro-5α-cholestan-6-one (VII)	302	+18	1·90	0·3
5-Bromo-5α-cholestan-6-one (XIII)	308	+24	2·10	0·5
5-Hydroxy-5α-cholestan-6-one (IV)	305	+21	—	—
3β-Acetoxy-5α-cholestan-6-one	280	—	1·6	—
3β-Acetoxy-5-bromo-5α-cholestan-6-one	308	+28	1·9	0·3
3β-Acetoxy-5-hydroxy-5α-cholestan-6-one	300	+20	1·77	0·17

Grasshof [1] found that on distillation at 290°/15 mm. the chloro-ketone gave a halogen-free ketone, m. p. 96°, $[\alpha]_D$ +5° (*c* 0·7 in C_6H_6) (oxime, m. p. 191—192°), regarded as derived from 4ξ-chloro-5α-cholestan-6-one (VIII) and assigned the structure 5α-cholest-3-en-6-one because its ultraviolet absorption spectrum failed to show the maximum at 240 mμ characteristic of αβ-unsaturated ketones. He found apparent confirmation for his view since the ketone, on treatment with hydrogen and palladium black in acetic acid for several hours, gave 5α-cholestan-6-one, m. p. 98°, $[\alpha]_D$ −9° (*c* 1·0 in C_6H_6) (oxime, m. p. 196—197°), identical with a genuine specimen prepared from 6-nitrocholest-5-ene by Windaus's method.[8]

Because the chloro-ketone has the structure (VII), and not (VIII), we repeated its vacuum-pyrolysis. Hydrogen chloride (0·96 mol.) was eliminated but the principal product (50%) was the saturated compound 5α-cholestan-6-one (X). Grasshof [1] gives no figure for the volume of hydrogen absorbed in his "hydrogenation" with palladium, neither does he appear to have determined the m. p. of a mixture of his pyro-ketone, $[\alpha]_D$ +5°, and its supposed hydrogenation product, $[\alpha]_D$ −9°; clearly they are both 5α-cholestan-6-one,[4,8] m. p. 98°, $[\alpha]_D$ −7°.

[6] Plattner, Petrzilka, and Lang, *Helv. Chim. Acta*, 1944, **27**, 513.
[7] Cookson, *J.*, 1954, 282; Cookson and Dandegaonker, *ibid.*, 1955, 352.
[8] Windaus, *Ber.*, 1920, **53**, 490.

The production of 5α-cholestan-6-one from 5-chloro-5α-cholestan-6-one by vacuum-pyrolysis is surprising and suggests a mechanism involving radicals, *e.g.*, (IX), since dismutation can then lead to a saturated unimolecular product (X) as shown. We



have been unable chromatographically to isolate cholest-4-en-6-one [4] (XI), $\lambda_{max.}$ 243 mμ, log ε 3·80, from the pyrolysis product, although the mother-liquors from the fractions yielding 5α-cholestan-6-one showed an absorption maximum of low intensity at 245 mμ. We have, however, obtained in about 15% yield a highly insoluble substance, m. p. 291°, $[\alpha]_D$ +33°, which may be derived from cholest-4-en-6-one by abstraction of hydrogen and subsequent dimerisation, and possess the structure (XII); the substance (mol. wt. 731) showed in its infrared absorption spectrum peaks at 1613 and 1680 cm.$^{-1}$ which are typical of αβ-unsaturated ketones [cf. cholest-4-en-3-one, 1614 and 1675 cm.$^{-1}$],[9] and in its ultraviolet absorption spectrum a single band with $\lambda_{max.}$ 250 mμ, log ε 4·0, which is consistent with the presence of two identical αβ-unsaturated ketone groupings although the maximum is displaced 8 mμ from that found for cholest-4-en-6-one [4] at 243 mμ (log ε 3·80) (calc. 242 mμ), and a somewhat higher extinction coefficient might have been expected. Owing to its insolubility, ketonic derivatives of the substance (XII?) could not be prepared and it resisted reduction by lithium aluminium hydride, and with platinum oxide in a variety of solvents.

5α-Cholestan-6-one (X) on monobromination in acetic acid at 20°, and 5-hydroxy-5α-cholestan-6-one (IV) on treatment with hydrogen bromide in chloroform at 20°, afforded a mixture of the 5α-bromo-ketone (XIII), the 7α-bromo-ketone (XVII), and the 7 : 7-dibromo-ketone (XX). The 5α-bromo-ketone (XIII; cf. VII) was also prepared from the 5β : 6β-epoxide (V); this on treatment with hydrogen bromide in acetic acid gave 5α-bromo-5α-cholestan-6β-ol (as VI), which could not be obtained crystalline but on treatment with zinc in acetic acid yielded cholest-5-ene (I) and on oxidation with chromium trioxide in acetic acid at 15° gave the 5α-bromo-ketone (XIII). For completeness, it should be stated that the 5α : 6α-epoxide (II) with hydrogen bromide in acetic acid furnished 5α-hydroxy-5α-cholestan-6β-yl bromide (as III with OR replaced by Br), converted by treatment with zinc in acetic acid into cholest-5-ene (I).

In the foregoing brominations the 5-bromo-5α-cholestan-6-one (XIII) is formed initially and converted in the presence of hydrogen bromide, by reduction and re-bromination [7] under thermodynamic control,[10] into 7α-bromo-5α-cholestan-6-one (XVII). On reduction with sodium borohydride, the 7α-bromo-ketone (XVII) gave a mixture of the 7α-bromo-6α- (XVI) and the 7α-bromo-6β-alcohol (XVIII); under the usual alkaline conditions of the reaction, these were in part dehydrobrominated, and passed respectively into 5α-cholestan-6-one (X) and 6β : 7β-epoxy-5α-cholestane (XIX), which was reduced by

[9] R. N. Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.
[10] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175.

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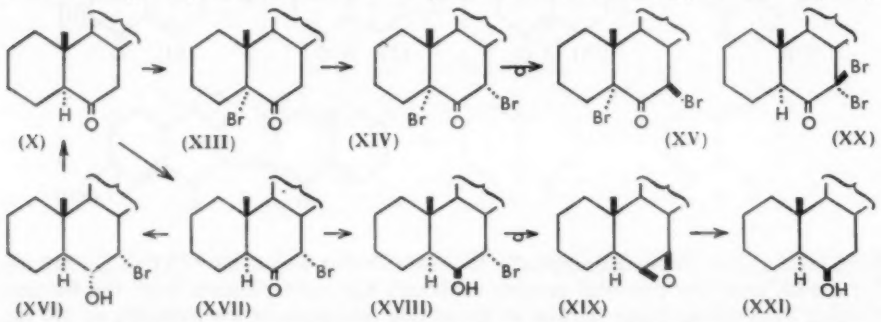
lithium aluminium hydride to 5α-cholestan-6β-ol (XXI). The 7α-bromo-6α-alcohol (XVI) afforded cholest-6-ene [11] when treated with zinc and acetic acid.

Dibromination of 5α-cholestan-6-one (X) in acetic acid afforded as the initial product of kinetic control 5 : 7α-dibromo-5α-cholestan-6-one (XIV) (a *cis*-2 : 6-dibromo*cyclo*hexan-1-one of fixed diaxial conformation). In the presence of hydrogen bromide the 5α : 7α-dibromo-ketone passed into the thermodynamically more stable 5α : 7β-dibromo-5α-cholestan-6-one (XV) (a *trans*-2 : 6-dibromo*cyclo*hexan-1-one of fixed axial–equatorial conformation), a crystalline material of m. p. 40° which is accordingly difficult to purify.



The formation, in small amounts, of the 7 : 7-dibromo-ketone (XX) appears to involve a relatively fast bromination of the axial 7α-hydrogen atom in the labile 7β-bromo-epimeride of (XVII), which is expected to be present to the extent of 2% in the equilibrium mixture. The stability of the 7 : 7-dibromo-ketone (XX) in the presence of hydrogen bromide is interesting. Since 2 : 2-dibromo-5α-cholestan-3-one is rapidly converted by dry hydrogen bromide into 2α : 4α-dibromo-5α-cholestan-3-one, conversion of the 7 : 7-dibromo-ketone into the 5α : 7β-dibromo-ketone (XV) might have been expected. The stability of the 7 : 7-dibromo-ketone (XX) may arise from the circumstance that the axial 7α-bromine atom is subject to repulsive 1 : 3-interaction with only three axial hydrogen atoms, whereas in the 5α : 7β-dibromo-ketone (XV) the axial 5α-bromine atom is subject to four such repulsive 1 : 3-interactions.

The structures assigned to the above bromo-ketones are supported by the values found in the ultraviolet absorption spectra for $\Delta\lambda_{max.}$ and $\Delta \log \varepsilon$,[7] and for the displacement

TABLE 2.

	$\lambda_{max.}$	$\Delta\lambda_{max.}$	log ε	Δ log ε	$\nu_{max.}$	$\Delta\nu_{max.}$
5α-Cholestan-6-one (X)	284	—	1·6	—	1711	—
5α-Chloro-5α-cholestan-6-one (VII)	302	+18	1·9	0·3	1715 †	+ 4
5α-Bromo-5α-cholestan-6-one (XIII)	308	+24	2·1	0·5	1712	+ 1
7α-Bromo-5α-cholestan-6-one (XVII)	308	+24	2·18	0·6	1711	0
5α : 7α-Dibromo-5α-cholestan-6-one (XIV)	334	+50	2·1	0·5	1713	+ 2
5α : 7β-Dibromo-5α-cholestan-6-one (XV)	— *	—	— *	—	1725	+14
7 : 7-Dibromo-5α-cholestan-6-one (XX)	292	+ 8	1·70	0·1	1725	+14
3β-Acetoxy-5α-cholestan-6-one	280	—	1·6	—	1711	—
3β-Acetoxy-5α-bromo-5α-cholestan-6-one	308	+28	2·1	0·5	1711	0
3β-Acetoxy-7α-bromo-5α-cholestan-6-one	310	+30	2·2	0·6	1713	+ 2
3β-Acetoxy-5α : 7α-dibromo-5α-cholestan-6-one	340	+60	2·2	0·6	1708	− 3
3β-Acetoxy-5α : 7β-dibromo-5α-cholestan-6-one	305	+25	2·1	0·5	1727	+16

The values of $\nu_{max.}$ for (X), (XIV), and (XV) in $CHCl_3$ were 1702, 1704, and 1716 cm.$^{-1}$. * No definite peak, but an inflection at ~315 mμ. † Since this paper was written $\nu_{max.}$ for (VII) in CS_2 has been reported as 1718 cm.$^{-1}$ ($\Delta\lambda = 4$) by Cummins and Page (*J.*, 1957, 3847), who have also measured the frequency of the low-frequency "halogen-sensitive" band at 756 cm.$^{-1}$ and so confirmed the axial conformation of the C–Cl linkage.

$\Delta\nu_{max.}$ of the carbonyl stretching frequency [9,10] in the infrared absorption spectra. These values are collected in Table 2, which also gives the values for the 3β-acetoxy-analogues ($\lambda_{max.}$ are for EtOH solutions, $\nu_{max.}$ for CCl_4).

[11] Reichstein and Shoppee, *Discuss. Faraday Soc.*, 1949, **7**, 205.

Experimental

For general experimental directions, see *J.*, 1957, 4364. Ultraviolet absorption spectra were determined for EtOH solutions in a Hilger Uvispek spectrophotometer; infrared absorption spectra were measured on a Perkin-Elmer Model 21 double-beam instrument. $[\alpha]_D$ are in $CHCl_3$, unless otherwise stated. Alumina was Spence type H (activity ~II).

5 : 6β-*Epoxy*-5β-*cholestane* (V).—Cholest-5-ene (m. p. 90°; 5 g.) in benzene (150 c.c.) was treated with a benzene solution of perbenzoic acid (1·2 mol.) at 0° for 3·5 days. The product, isolated in the usual way, was chromatographed on aluminium oxide (150 g.) in pentane. Elution with pentane (4 × 75 c.c.) gave 5 : 6β-epoxy-5β-cholestane (300 mg.), m. p. 58° (lit.,[3] m. p. 53°) after crystallisation from ethanol; further elution with pentane and benzene–pentane (1 : 9) gave 5 : 6α-epoxy-5α-cholestane, m. p. 80°.

5-*Chloro*-5α-*cholestan*-6β-*ol* (VI).—The 5β : 6β-epoxide (V) (83 mg.) in chloroform (10 c.c.) was treated with dry hydrogen chloride at 15° for 1 hr., and the solution left overnight. The usual working up afforded an oil, which on crystallisation from acetone–methanol gave 5-*chloro*-5α-*cholestan*-6β-ol (70 mg.), m. p. 108—109°, $[\alpha]_D$ −22° (*c* 0·7) [Found (after drying at 40°/0·01 mm. for 12 hr.): C, 76·95; H, 11·2. $C_{27}H_{47}OCl$ requires C, 76·8; H, 11·0%].

5-*Chloro*-5α-*cholestan*-6-*one* (VII).—(*a*) The 5α-chloro-6β-alcohol (VI) (61 mg.) in 1 : 2 ether–acetic acid (6 c.c.) was oxidised with a 2% solution of chromium trioxide in acetic acid (1·0 c.c. ≡ 2 g.-atoms of O) at 15° for 18 hr. Excess of chromium trioxide was destroyed by addition of methanol, the solution diluted with water, and the precipitate filtered off, washed with water, and dried. Recrystallisation from acetone–methanol gave 5-chloro-5α-cholestan-6-one (40 mg.), m. p. 116°, $[\alpha]_D$ −102° (*c* 0·7) [Found (after drying at 55°/0·01 mm. for 10 hr.): C, 76·9; H, 10·7. Calc. for $C_{27}H_{45}OCl$: C, 77·0; H, 10·7%].

(*b*) 5-Hydroxy-5α-cholestan-6-one (IV) (m. p. 150°; 5 g.) in chloroform (100 c.c.) was treated with dry hydrogen chloride at 20° for 1 hr.; working up in the usual way afforded an oil, which crystallised readily from acetone to give 5-chloro-5α-cholestan-6-one (4 g.), m. p. and mixed m. p. 116°, $[\alpha]_D$ −104° (*c* 1·2). The infrared spectra of the two preparations were identical.

Pyrolysis of 5-*Chloro*-5α-*cholestan*-6-*one* (VII).—The chloro-ketone (4·60 g.) was distilled at 295°/10 mm. and the distillate re-distilled at 295°/10 mm. into a second receiver; the gaseous products were passed into 0·1N-sodium hydroxide (200 c.c.) and subsequent titration showed that 0·96 mol. of hydrogen chloride had been evolved. The final distillate was chromatographed on aluminium oxide (140 g.) in light petroleum. Elution with light petroleum and with benzene–light petroleum (1 : 9) furnished 5α-cholestan-6-one [5,6] (2·0 g.), m. p. and mixed m. p. 98°, $[\alpha]_D$ −7° (*c* 1·0); the mother-liquors gave further small quantities of the saturated ketone, but cholest-4-en-6-one could not be isolated although an absorption maximum of low intensity at 245 mμ was observed. Elution with benzene gave an oil, which on crystallisation from chloroform–ethyl acetate yielded a *substance* (XII?) (650 mg.), m. p. 291°, $[\alpha]_D$ +33° (*c* 0·8), $\lambda_{max.}$ 250 mμ (log ε 4·0), $\nu_{max.}$ (in $CHCl_3$) 1613 and 1680 cm.$^{-1}$ [Found (after drying at 80°/0·01 mm. for 6 hr.): C, 84·0, 84·4; H, 9·8, 10·1; O, 5·2%; *M* (Rast), 731. $C_{54}H_{88}O_2$ requires C, 84·3; H, 11·5; O, 4·2%; *M*, 768], giving a yellow colour with tetranitromethane–chloroform and a negative Beilstein test. In another experiment, the chloro-ketone (3 g.) gave 5α-cholestan-6-one (1·8 g. crude; 1·5 g. pure) and the dimer (XII?) (360 mg.). Pyrolysed in an atmosphere of nitrogen, the chloro-ketone (3 g.) gave 5α-cholestan-6-one (1·3 g.) and the dimer (XII?) (400 mg.).

4β-*Chloro*-5α-*cholestan*-6-*one* (VIII).—Cholest-4-en-6-one (m. p. 108°; 0·5 g.) in chloroform (20 c.c.) was treated with dry hydrogen chloride for 0·75 hr.; working up in the usual way afforded an oil which crystallised readily from acetone to give 4β-*chloro*-5α-*cholestan*-6-*one* (490 mg.) as needles, m. p. 173—174° [Found (after drying at 25°/0·01 mm. for 8 hr.): C, 76·85; H, 10·7. $C_{27}H_{45}OCl$ requires C, 77·0; H, 10·7%].

5α-*Bromo*-5α-*cholestan*-6-*one* (XIII).—(*a*) The 5β : 6β-epoxide (V) (100 mg.) in acetic acid was treated with a 5% solution of hydrogen bromide in acetic acid (2 c.c.) at 15° for 1 hr. The solution was worked up in the usual way, giving an oil. This crude 5-bromo-5α-cholestan-6β-ol in acetic acid (10 c.c.) was refluxed with zinc for 1 hr., to give cholest-5-ene, m. p. and mixed m. p. 88—90° (from acetone–methanol); the residue of the crude bromohydrin in acetic acid (3 c.c.) was oxidised with a 2% solution of chromium trioxide in acetic acid (2 c.c.) at 15° for 18 hr. Excess of the reagent was destroyed by methanol, the solution diluted and extracted

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with ether, and the product isolated in the usual manner, to furnish an oil, which crystallised from acetone–methanol. 5-Bromo-5α-cholestan-6-one (40 mg.) had m. p. and mixed m. p. 101°, $[\alpha]_D$ −146° (*c* 1·2).

(*b*) 5α-Cholestan-6-one (500 mg.) in ether–acetic acid (1 : 1; 20 c.c.) was treated with a 10% solution of bromine in acetic acid (2 c.c., 1·1 mol.) and a few drops of a solution of hydrogen bromide in acetic acid, and kept at 15° for 1 hr. The colourless solution, after the usual working up, yielded 5-bromo-5α-cholestan-6-one (300 mg.), m. p. and mixed m. p. 101°, $[\alpha]_D$ −145° (*c* 1·2) (from acetone–methanol) [Found (after drying at 40°/0·01 mm. for 10 hr.): C, 69·4; H, 9·7. Calc. for $C_{27}H_{45}OBr$: C, 69·6; H, 9·75%]. Henbest and Wrigley [11a] give m.p. 101—102°, $[\alpha]_D$ −134°.

5-Bromo- (XIII), *7α-Bromo-* (XVII), *and 7 : 7-Dibromo-5α-cholestan-6-one* (XX).—5-Hydroxy-5α-cholestan-6-one (IV) (3 g.) in chloroform (100 c.c.) was treated with dry hydrogen bromide at 20° for 2 hr. and left overnight. Working up in the usual way gave an oil, which was chromatographed on aluminium oxide (90 g.) in light petroleum. Elution with light petroleum afforded an oil, which crystallised from ethanol, to give *7α-bromo-5α-cholestan-6-one* (1·3 g.), m. p. 82°, $[\alpha]_D$ +51° (*c* 1·1) [Found (after drying at 20°/0·01 mm. for 12 hr.): C, 69·5; H, 9·8. $C_{27}H_{45}OBr$ requires C, 69·6; H, 9·75%]. Elution with benzene–light petroleum (1 : 9) gave material which crystallised readily from ethanol, to yield 5-bromo-5α-cholestan-6-one (600 mg.), m. p. and mixed m. p. 101°. Elution with benzene–light petroleum (1 : 4) gave an oil (600 mg.), from which by repeated recrystallisation there was obtained *7 : 7-dibromo-5α-cholestan-6-one* (45 mg.), m. p. 167—168°, $[\alpha]_D$ −28° (*c* 0·85) [Found (after drying at 40°/0·01 mm. for 10 hr.): C, 60·4; H, 7·9. $C_{27}H_{44}OBr_2$ requies C, 59·6; H, 8·15%].

Reduction of 7α-Bromo-5α-cholestan-6-one (XVII).—To a solution of the 7α-bromo-ketone (830 mg.) in ether (100 c.c.) was added one of sodium borohydride (350 mg.) in methanol (50 c.c.), and the mixture kept at 15° for 18 hr. The product, isolated in the usual way, was an oil which was chromatographed on neutralised aluminium oxide [11] (28 g.) in light petroleum. Elution with light petroleum furnished an oil (130 mg.) which crystallised from ethanol, to give 6β : 7β-*epoxy-5α-cholestane*, m. p. 106—108°, $[\alpha]_D$ −10° (*c* 1·05) [Found (after drying at 40°/0·01 mm. for 12 hr.): C, 83·3; H, 11·8. $C_{27}H_{46}O$ requires C, 83·8; H, 12·0%]. Elution with benzene–light petroleum (1 : 4 and 3 : 7) gave an oil (90 mg.), which by crystallisation from ethanol afforded 5α-cholestan-6-one, m. p. and mixed m. p. 98°. Elution with benzene–light petroleum (1 : 1), and with benzene, gave an oil (200 mg.), which by crystallisation from ethanol gave *7α-bromo-6α-hydroxy-5α-cholestane* (XVI), m. p. 168°, $[\alpha]_D$ −13° (*c* 1·0) [Found (after drying at 60°/0·01 mm. for 6 hr.): C, 68·9; H, 9·9. $C_{27}H_{47}OBr$ requires C, 69·3; H, 10·15%]. Finally, elution with ether–benzene mixtures and with ether gave material (90 mg.), which on crystallisation from ethanol gave an unidentified substance, m. p. 233—235°, $[\alpha]_D$ −20° (*c* 1·0) [Found (after drying at 60°/0·01 mm. for 6 hr.): C, 79·5; H, 11·2%].

Dehydrobromination and Dehypobromination of the 7α-Bromo-6α-alcohol (XVI).—(*a*) The bromohydrin (40 mg.) was dissolved in a solution of potassium hydroxide (150 mg.) in methanol (8 c.c.) and the solution refluxed for 5 hr. The solution was diluted and the resulting precipitate filtered off, washed with water, and dried. Recrystallisation from ethanol gave 5α-cholestan-6-one, m. p. and mixed m. p. 98°.

(*b*) The bromohydrin (65 mg.) was refluxed with zinc dust (300 mg.) in acetic acid (15 c.c.) for 6 hr.; the warm solution was filtered off, acetic acid largely removed at 10 mm., and the product extracted with ether. The usual procedure gave an oil, which crystallised from acetone to give 5α-cholest-6-ene,[12] m. p. 86—87°, $[\alpha]_D$ −91° (*c* 1·07).

5α-Cholestan-6β-ol (XXI).—The 6β : 7β-epoxide (50 mg.) in ether (15 c.c.) was added to a solution of lithium aluminium hydride (30 mg.) in ether (10 c.c.), and the mixture refluxed for 4 hr. Excess of the reagent was decomposed with ice and 2N-sulphuric acid, and the product isolated in the usual way. The resulting oil crystallised with difficulty from methanol, to give 5α-cholestan-6β-ol, m. p. 78—82°, mixed m. p. with authentic 5α-cholestan-6β-ol,[13] 80—82°.

5 : 7α-Dibromo-5α-cholestan-6-one (XIV).—5α-Cholestan-6-one (670 mg.) was dissolved in acetic acid (40 c.c.) and treated with a 10% solution of bromine in acetic acid (6·2 c.c., 2·2 mol.). After 2 hr. at 15°, the colourless solution was worked up in the usual way, to give an oil, which was chromatographed on neutralised aluminium oxide [11] (20 g.). Elution with light petroleum

[11a] Henbest and Wrigley, *J.*, 1958, 4596.
[12] Fischer, Lardelli, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 1577.
[13] Shoppee and Summers, *J.*, 1952, 1786, 3361.

gave an oil (240 mg.), which crystallised with difficulty from ethanol, to give 5 : 7α-*dibromo*-5α-*cholestan*-6-*one*, m. p. 115°, $[\alpha]_D$ −101° (*c* 0·9) [Found (after drying at 40°/0·01 mm. for 8 hr.): C, 60·0; H, 8·3. $C_{27}H_{44}OBr_2$ requires C, 59·55; H, 8·15%]. Elution with benzene–light petroleum furnished some 5α-cholestan-6-one (negative Beilstein test).

5 : 7β-*Dibromo*-5α-*cholestan*-6-*one* (XV).—5α-Cholestan-6-one (460 mg.) in acetic acid (50 c.c.) was treated with a 10% solution of bromine in acetic acid (4 c.c., 2·2 mol.), and with a solution of hydrogen bromide in acetic acid (0·5 c.c.) at 15°. After being kept overnight at 20°, the colourless solution was diluted with water (50 c.c.), and the precipitate filtered off, washed with water, and dried, to afford 5 : 7β-dibromo-5α-cholestan-6-one, m. p. ~40°, $[\alpha]_D$ −12° (*c* 0·8), which could not satisfactorily be crystallised but gave satisfactory analytical figures [Found (after drying at 15°/0·01 mm. for 18 hr.): C, 59·3; H, 8·05. $C_{27}H_{44}OBr_2$ requires C, 59·55; H, 8·15%].

5-*Hydroxy*-5α-*cholestan*-6β-*yl Chloride and Bromide*.—5 : 6α-Epoxy-5α-cholestane in chloroform was treated with dry hydrogen chloride at 15° for 1 hr., and the solution set aside overnight. The usual isolation furnished material, which on crystallisation from acetone gave 5-*hydroxy*-5α-*cholestan*-6β-*yl chloride*, m. p. 119°, $[\alpha]_D$ −6° (*c* 1·2) [Found (after drying at 20°/0·01 mm. for 7 hr.): C, 76·45; H, 11·2. $C_{27}H_{47}OCl$ requires C, 76·8; H, 11·0%]. Use of hydrogen bromide similarly gave 5-*hydroxy*-5α-*cholestan*-6β-*yl bromide*, m. p. 109—110°, $[\alpha]_D$ −11° (*c* 1·35), after crystallisation from acetone [Found (after drying at 20°/0·01 mm. for 6 hr.): C, 69·5; H, 10·05. $C_{27}H_{47}OBr$ requires C, 69·5; H, 9·95%].

One of us (R. H. J.) acknowledges the financial support of the Department of Scientific and Industrial Research and of the Commonwealth Scientific and Industrial Research Organisation. We thank Nicholas (Pharmaceuticals) Pty. Ltd., Melbourne, for a gift of cholesterol, Dr. R. I. Cox, Department of Veterinary Physiology, the University of Sydney, for the infrared spectra, and Miss B. Stevenson of the Department of Organic Chemistry, the University of Sydney, for the microanalyses.

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330. *Addition Compounds of Gallium Trichloride. Part V.*[1] *Ionic* 1 : 1 *and* 1 : 2 *Complexes with Pyridine.*

By N. N. GREENWOOD and K. WADE.

The new compounds $GaCl_3,C_5H_5N$ (m. p. 126°) and $GaCl_3,2C_5H_5N$ (m. p. 113°) have been established by phase studies on the system gallium trichloride–pyridine. The 1 : 1 complex distils unchanged at low pressures but the 1 : 2 complex loses pyridine readily under these conditions. Both complexes form ionic melts and their conductivity, viscosity, density, and surface tension have been determined over a range of temperatures. The vapour pressure of the 1 : 1 complex has also been studied. These properties are compared with those of related complexes and arguments are presented which suggest that the structures of the complexes are $[(C_5H_5N)_2GaCl_2]^+GaCl_4^-$ and $[(C_5H_5N)_2GaCl_2]^+Cl^-$.

WHEN pyridine is distilled in vacuum on to gallium trichloride there is a rapid exothermic reaction which yields either a 1 : 1 or 1 : 2 co-ordination compound, depending on the molar ratio of the reactants. The 1 : 1 compound is the more stable but both can be investigated by means of the techniques described earlier.[1] There is no evidence for a 1 : 3 compound such as has been reported for indium trichloride,[2] thallium trichloride,[3,4] and thallium tribromide [4] with pyridine.

[1] Part IV, Greenwood, Perkins, and Wade, *J.*, 1957, 4345.
[2] Renz, *Z. anorg. Chem.*, 1903, **36**, 101.
[3] Meyer, *ibid.*, 1900, **24**, 321; Renz, *Ber.*, 1902, **35**, 1110.
[4] Abbott, *Iowa State Coll. J. Sci.*, 1943, **18**, 3.

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The specific electrical conductivity, viscosity, density, and surface tension of the 1 : 1 and the 1 : 2 complex, as well as the vapour pressure of the 1 : 1 complex have been determined over a range of temperature and from these have been derived the molar conductivity, reduced conductivity, activation energies of conduction and viscous flow, surface free energy, Eötvös constant, parachor, and heat of evaporation. Both complexes dissociate considerably into ions but an unequivocal assignment of structure was not possible since electrolysis of the melt resulted in an irreversible charring process at the anode, no reaction being visible at the cathode. However, comparison of the results with those obtained on related complexes favours the suggestion that the 1 : 1 compound is dipyridinedichlorogallium tetrachlorogallate $[py_2GaCl_2]^+GaCl_4^-$, the 1 : 2 compound being either the corresponding chloride $[py_2GaCl_2]^+Cl^-$ or the tetrachlorogallate $[py_4GaCl_2]^+GaCl_4^-$.

Experimental and Results

Gallium trichloride, m. p. 77·8°, was prepared, purified, and handled as described in Part I.[5] Pyridine, m. p. −41°, b. p. 115·3°, was dried by refluxing it for several hours over potassium

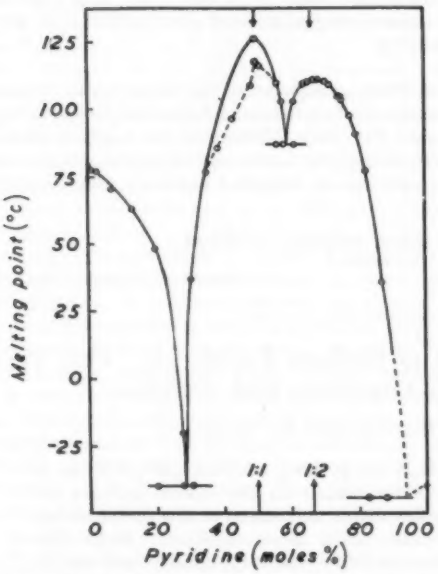


Fig. 1. *Phase diagram of the system* $GaCl_3$–C_5H_5N.

hydroxide or barium oxide and then fractionating it in a 60 cm. column packed with glass helices. It was subsequently handled in a vacuum line. The methods used to measure the electrical conductivity,[6,7] viscosity,[8,9] density, and surface tension [9] have been described earlier.

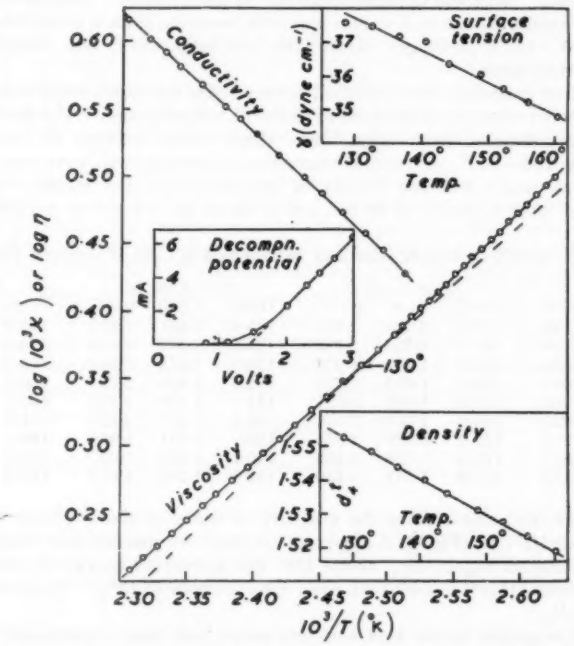
The vapour pressure of gallium trichloride–pyridine was obtained by sealing the complex into a side limb attached to a U-tube 8 mm. in diameter containing mercury. The mercury was degassed by heating it to 200—250° under dynamic vacuum before sealing off both arms of the manometer; the complex was likewise degassed by melting it under dynamic vacuum. The whole apparatus was then immersed in a thermostatted oil bath in a transparent Dewar vessel. Differences in levels were read on a cathetometer to ±0·02 mm. and corrected for thermal expansion of the mercury.

[5] Greenwood and Wade, *J.*, 1956, 1527.
[6] Greenwood and Worrall, *J. Inorg. Nuclear Chem.*, 1957, **3**, 357.
[7] Greenwood and Wade, *J.*, 1957, 1516.
[8] *Idem*, *J. Sci. Instrum.*, 1957, **34**, 288.
[9] *Idem*, *J. Inorg. Nuclear Chem.*, 1957, **3**, 349.

Results.—The m. p. diagram of the system gallium trichloride–pyridine is shown in Fig. 1. There are well-defined maxima at 50·0 and 66·7 moles % of pyridine and eutectics at 28·5% (−40°), 59·0% (86°), and 93% (−45°). The 1 : 1 compound melted at 119° when prepared during these phase studies because of slight decomposition or the presence of impurities introduced during the successive addition or removal of weighed amounts of pyridine from the vacuum line. Direct preparations when purified by fractional freezing melted at 126°.

The flatter maximum of the 1 : 2 complex at 113° indicates that this compound is more dissociated in the liquid phase than is the 1 : 1 complex. This is consistent with the fact that gallium trichloride absorbs pyridine with considerable evolution of heat up to the equimolar ratio but beyond this pyridine must be added by cooling the reaction mixture in a bath of ethanol–solid carbon dioxide. Pyridine in excess of the 1 : 1 ratio could always be removed

FIG. 2. *Properties of molten* $GaCl_3,C_5H_5N$.



from the molten mixture by vacuum distillation and this afforded an alternative means of preparing the pure 1 : 1 compound which could itself be sublimed or distilled *in vacuo* without decomposition.

TABLE 1. *Electrical conductivity of* $GaCl_3,C_5H_5N$ *between* 125° *and* 160°.

No.	Temp.	$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)	$\mu = \kappa V_M$ (cm.^{3} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{3} cP ohm^{-1} mole^{-1})	No.	Temp.	$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)	$\mu = \kappa V_M$ (cm.^{3} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{3} cP ohm^{-1} mole^{-1})
8	124·8°	2·677	0·4387	1·076	4	145·1°	3·479	0·5785	1·103
9	127·5	2·784	0·4573	1·081	13	147·4	3·561	0·5929	1·103
7	129·7	2·869	0·4719	1·082	3	150·2	3·697	0·6167	1·111
10	132·3	2·968	0·4891	1·086	14	153·2	3·807	0·6365	1·107
6	135·0	3·074	0·5075	1·089	2	155·2	3·906	0·6542	1·113
11	137·2	3·157	0·5220	1·091	15	157·6	3·996	0·6702	1·114
5	140·1	3·281	0·5436	1·098	1	160·4	4·134	0·6947	1·120
12	143·0	3·394	0·5635	1·102					

The 1 : 1 *complex* $GaCl_3,C_5H_5N$. Gallium trichloride–pyridine was prepared on the 30 g. scale and purified by repeated fractional freezing in vessels attached directly to the conductivity cell, viscometer, or dilatometer, and consisted of white crystals, m. p. (sharp) 126°.

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The specific electrical conductivity, κ, which was reproducible and showed no variation over a period of 4 days, was measured in the temperature range 125—160°. Results, and the sequence of measurements, are in Table 1. At 126° the conductivity is $2{\cdot}725 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$ and this corresponds to a molar conductivity, μ, of 0·4472 cm.^{2} ohm^{-1} mole^{-1} and a reduced conductivity, $\mu\eta$, of 1·077 cm.^{2} cP ohm^{-1} mole^{-1}, where η is the dynamic viscosity of the molten complex in cP. The approximate constancy of the reduced conductivity indicates that the molar conductivity is inversely proportional to the viscosity. As shown in Fig. 2, a plot of log κ against $1/T$ (°K) is very slightly curved, the mean slope corresponding to an activation energy for conduction, E_κ, of 4·16 kcal. mole^{-1}. The corresponding plot of log μ is also slightly curved and leads to a mean activation energy, E_μ, of 4·39 kcal. mole^{-1}.

A d.c. current–voltage experiment carried out on the complex between platinum electrodes at 133° indicated a decomposition potential of $1{\cdot}4_3$ v (Fig. 2). Above 1·1 v (0·28 mA) charring occurred at the anode; there was no visible reaction at the cathode. Because of this irreversible breakdown at the anode, back-e.m.f. values had little meaning since a reversible potential could not be established; after prolonged electrolysis the back-e.m.f. was about 0·3 v but this decreased rapidly with time.

The viscosity was measured in a sealed all-glass viscometer which employed the weir system to maintain a constant mean head of liquid at different temperatures. The kinematic viscosity, ν (centistoke), was computed from efflux times which varied between 60 and 110 sec. in the temperature range 108—160°. Dynamic viscosities, η (centipoise), were then obtained from the relation $\eta = \nu d$, where d is the density of the complex. The results, which showed no variation with time over a period of 36 hr., are in Table 2. At the m. p., 126°, the dynamic

TABLE 2. *Viscosity of supercooled and molten* $GaCl_3,C_5H_5N$ *between* 108° *and* 160°.

Supercooled			Supercooled			Above m. p.			Above m. p.		
Temp.	ν (cS)	η (cP)	Temp.	ν (cS)	η (cP)	Temp.	ν (cS)	η (cP)	Temp.	ν (cS)	η (cP)
107·9°	2·006	3·158	116·9°	1·758	2·751	125·9°	1·551	2·412	144·2°	1·255	1·928
108·9	1·977	3·111	117·9	1·734	2·711	128·0	1·513	2·350	146·2	1·228	1·884
109·9	1·949	3·065	118·9	1·710	2·673	130·0	1·475	2·287	148·2	1·202	1·841
110·9	1·915	3·010	119·9	1·683	2·629	132·0	1·439	2·228	150·2	1·178	1·801
111·9	1·888	2·965	120·9	1·663	2·595	134·0	1·404	2·172	152·2	1·152	1·759
112·9	1·861	2·921	121·9	1·639	2·556	136·1	1·373	2·120	154·2	1·127	1·719
113·9	1·831	2·872	122·9	1·619	2·524	138·1	1·341	2·069	156·2	1·106	1·684
114·9	1·809	2·835	123·9	1·596	2·486	140·1	1·312	2·020	158·2	1·085	1·650
115·9	1·782	2·790	124·9	1·574	2·450	142·1	1·283	1·973	160·2	1·064	1·616

viscosity is $2{\cdot}40_8$ cP, *i.e.*, about twice the viscosity of water at room temperature. From the plot of log η against $1/T$ (°K) (Fig. 2) it appears that there is a discontinous change in slope near the m. p. as the complex supercools; above 130° the activation energy of viscous flow, E_η, is 3·96 kcal. mole^{-1}, below this it is 4·47 kcal. mole^{-1}, an increase of 13%. These values are similar to those of E_κ and E_μ.

The density of a sample of the 1 : 1 complex which had been vacuum-distilled at temperatures well above the m. p. was virtually identical with that obtained on a sample purified by fractional refreezing, a fact which emphasizes the thermal stability of the compound:

$$\text{Distilled sample: } d_4^t = 1{\cdot}5563 - 1{\cdot}068 \times 10^{-3}(t - 125)$$

$$\text{Recrystallized sample: } d_4^t = 1{\cdot}5557 - 1{\cdot}070 \times 10^{-3}(t - 125)$$

Individual results from the first run, which extended from 125° to 160°, are shown graphically in Fig. 2.

The variation of surface tension in the same temperature range is given by

$$\gamma = 38{\cdot}2 - 0{\cdot}097(t - 125) \text{ dyne cm.}^{-1}$$

The corresponding equation for the molar surface free energy, ω, is

$$\omega = \gamma V_M^{2/3} = 1143 - 2{\cdot}34(t - 125) \text{ erg mole}^{-2/3}$$

In these equations V_M is the molar volume and the constant 2·34 is the Eötvös constant k. The parachor ($[P] = V_M\gamma^{1/4}$) is independent of temperature and has a mean value of 408·1 ($\pm$0·3 r.m.s.).

The vapour pressure of gallium trichloride–pyridine is $<10^{-1}$ mm. at the m. p. but rises to about 1 mm. at 175° and 10 mm. at 220°. The detailed results are given in Table 3 which also records the sequence of measurements as an indication of their reproducibility and the stability of the complex. The plot of log p against $1/T(°K)$ is slightly curved but has an average slope corresponding to a heat of vaporisation of 20·3 kcal. mole^{-1}. The ratio $\Delta H_{vap}/E_\eta$ has the

TABLE 3. *Vapour pressure of* $GaCl_3,C_5H_5N$ *between* 150° *and* 250°.

No.	Temp.	p (mm. Hg)	No.	Temp.	p (mm. Hg)	No.	Temp.	p (mm. Hg)	No.	Temp.	p (mm. Hg)
1	153·9°	0·36	4	183·6°	1·91	6	209·4°	5·83	20	233·0°	15·33
2	167·0	0·69	8	188·2	2·31	12	215·8	8·21	16	235·5	15·60
3	170·4	0·77	5	194·2	3·15	13	220·0	9·23	19	240·5	19·25
9	176·6	1·12	7	199·6	4·02	14	224·5	10·92	18	245·3	21·98
10	178·4	1·39	11	204·6	4·86	15	230·0	13·05	17	250·4	24·44

rather high value of 5·1. Another point of interest is that the vapour pressure curve extrapolates to a " boiling point " of about 350°; this may be compared with the approximate value obtained from the surface free-energy curve which extrapolates to a critical point ($\omega = 0$) of 615° and hence to a b. p. of about 320° if one uses the relation $(t_{b.p.} + 273) = (\frac{2}{3})(t_{c.p.} + 273)$. Neither extrapolation is expected to be particularly precise but both indicate similar values for the b. p.

These results on the 1 : 1 compound are discussed further below.

The 1 : 2 *complex* $GaCl_3,2C_5H_5N$. Gallium trichloride–dipyridine was prepared by the reaction of 7·435 g. of gallium trichloride with 6·682 g. of pyridine (mole ratio 1 : 2·0008). However, there was slight loss of pyridine during the subsequent manipulation of the complex and the m. p. was about 4° below the value of 113° obtained from the phase studies. This is unlikely to affect values of the other physical properties appreciably but the difficulties in handling this readily dissociating complex render the determination of its properties somewhat less accurate than those of the exceptionally stable 1 : 1 complex to which it tends to revert. In particular it was necessary to keep the gas space above the 1 : 2 complex as small as possible to minimize loss of pyridine from the liquid arising from the equilibrium

$$GaCl_3,2C_5H_5N \rightleftharpoons GaCl_3,C_5H_5N + C_5H_5N$$

The compound could frequently be cooled almost to room temperature before crystallization set in.

The electrical conductivity was measured in the range 103—136° and was reproducible to within 1 in 1000 at a given temperature during 5 hr. Recharging the cell with a different sample of complex also left the conductivity unchanged. Table 4 lists the results. For comparison with the 1 : 1 complex one can select values at 126°: the specific conductivity, κ, is

TABLE 4. *Electrical conductivity of molten and supercooled* $GaCl_3,2C_5H_5N$ *between* 103° *and* 136°.

No.	Temp.	$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)	$\mu = \kappa V_M$ (cm.^{2} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{2} cP ohm^{-1} mole^{-1})	No.	Temp.	$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)	$\mu = \kappa V_M$ (cm.^{2} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{2} cP ohm^{-1} mole^{-1})
5	103·2°	7·78	1·88	7·95	21	117·9°	10·54	2·59	6·46
7	103·6	7·85	1·90	7·90	12	119·6	10·83	2·67	6·31
8	105·6	8·23	1·99	7·65	20	122·1	11·23	2·77	6·11
6	106·8	8·46	2·05	7·51	13	123·8	11·49	2·85	5·99
4	107·1	8·61	2·09	7·56	19	126·7	11·98	2·98	5·77
9	108·7	8·86	2·15	7·32	14	128·0	12·12	3·02	5·66
3	110·3	9·16	2·23	7·14	18	130·3	12·47	3·11	5·49
10	112·3	9·54	2·33	6·95	15	132·2	12·70	3·18	5·38
2	114·3	9·90	2·42	6·74	17	133·8	12·91	3·24	5·28
11	115·8	10·20	2·50	6·63	16	135·7	13·11	3·29	5·14
1	117·9	10·53	2·59	6·45					

$11·86 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$, the molar conductivity, μ, is 2·95 cm.^{2} ohm^{-1} mole^{-1}, and the reduced conductivity, $\mu\eta$, is 5·82 cm.^{2} cP ohm^{-1} mole^{-1}. These figures show that the 1 : 2 complex conducts some 4—7 times better than the 1 : 1 complex, depending on the particular measure of conduction used (and the temperature).

XUM

The plot of log κ against $1/T$ (°K) is a smooth curve, the activation energy E_κ decreasing steadily from 6·86 kcal. mole^{-1} at the lower temperatures to 3·30 kcal. mole^{-1} at high temperatures. Similarly E_μ decreases from 7·64 to 3·59 kcal. mole^{-1}. At 126° $E_\kappa = 3·96$ and $E_\mu = 4·21$ kcal. mole^{-1}, values which are very close to those for the 1 : 1 complex (4·16 and 4·39 respectively).

The viscosity of gallium trichloride–dipyridine is given in Table 5. It was reproducible over a period of days and is similar to that of the 1 : 1 complex, the two quantities being identical at the m. p. of the 1 : 2 complex, 113°. However, the viscosity of the 1 : 2 complex changes more rapidly with temperature, E_η varying from 11·05 kcal. mole^{-1} at low temperatures to 7·78 kcal. mole^{-1} at high temperatures. At 126° $E_\eta = 7·80$ kcal. mole^{-1} (4·47 kcal. mole^{-1} for the 1 : 1 complex). The activation energy for viscous flow of the 1 : 2 complex is greater than for any other complex of gallium trichloride yet investigated though it is approached by the 1 : 2 complex with piperidine discussed in the following paper. Because the activation energy for conduction is not also abnormally large it follows that conductivity and viscosity are not strictly inversely proportional and $\mu\eta$ falls as the temperature rises (Table 4). This point will be amplified in the Discussion.

TABLE 5. *Viscosity of molten and supercooled* $GaCl_3,2C_5H_5N$ *between* 103° *and* 137°.

Temp.	ν (cs)	η (cP)	Temp.	ν (cs)	η (cP)	Temp.	ν (cs)	η (cP)	Temp.	ν (cs)	η (cP)
103·0°	3·077	4·262	113·0°	2·128	2·911	123·0°	1·589	2·148	133·0°	1·244	1·661
105·0	2·845	3·929	115·0	1·990	2·716	125·0	1·502	2·025	135·0	1·191	1·586
107·0	2·636	3·634	117·0	1·878	2·558	127·0	1·429	1·922	137·0	1·138	1·512
109·0	2·444	3·360	119·0	1·774	2·409	129·0	1·361	1·826			
111·0	2·275	3·119	121·0	1·672	2·265	131·0	1·295	1·734			

The density run was not as extensive as the others but the following equation was derived from results obtained between 92° and 107°:

$$d_4^t = 1·389 - 1·64 \times 10^{-3}(t - 100)$$

In the temperature range 92—102° the surface tension was about 50 dyne cm.$^{-1}$ and the parachor 640 but it is probable that these values are quite inaccurate owing to the depletion in pyridine of the surface layers of complex as a result of thermal dissociation, and little reliance is placed on them.

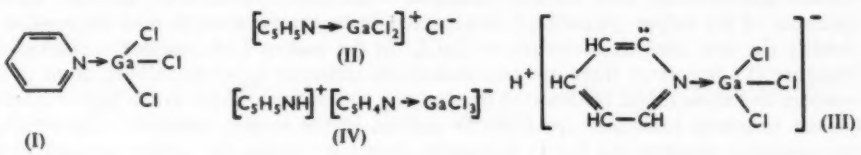
DISCUSSION

The most striking effect of complex formation in the system gallium trichloride–pyridine is the great increase in electrical conductivity. The published values for the specific conductivities of molten gallium trichloride [6] and pyridine [10] are 2×10^{-6} and 4×10^{-8} ohm^{-1} cm.$^{-1}$ respectively, whereas for the complexes near their m. p.s the values are 3×10^{-3} and 1×10^{-2}. It is therefore important to enquire what ions are present and to what extent the complexes are dissociated into kinetically free ions. In the absence of direct evidence probable structures for the complexes can be inferred by a process of elimination.

The simple formula (I) for the 1 : 1 complex is unsatisfactory since it leaves unexplained the high electrical conductivity and does not account for the ability of the complex to take up a further mole of pyridine, unless a pentaco-ordinate complex of gallium is postulated for the 1 : 2 compound. The similarity in m. p., conductivity, viscosity, and other physical properties of the two complexes suggests that their structures are similar. Ionization by separation of a chloride ion (II) is unlikely as it leaves the gallium atom electron-deficient in the presence of a strong electron donor, Cl^- (cf. Ga_2Cl_6). The cation $[C_5H_5N{\rightarrow}GaCl_2]^+$ in structure (II) could, however, be stabilized by the addition of a further molecule of pyridine to give $[(C_5H_5N)_2GaCl_2]^+Cl^-$, the structure suggested for the 1 : 2 complex (below). Structure (III) for the 1 : 1 complex involves ionization of an α-hydrogen atom from the pyridine molecule and is untenable for a variety of reasons. First, no gas

[10] Walden, Audrieth, and Birr, *Z. phys. Chem.*, 1932, **160**, *A*, 337.

is evolved during electrolysis of the molten complex, suggesting that hydrogen ions are absent. This evidence becomes more cogent when coupled with the analogous behaviour of the corresponding piperidine complex discussed in the following paper, for with piperidine there is no possibility that cathodic reduction of the ligand could remove the nascent hydrogen. Secondly, there is no apparent means of solvating the bare proton unless it be with a second undissociated molecule of complex as shown in structure (I); even



then, the only non-bonding electrons available for donation to the proton are those on the chlorine atoms. The situation is thus rather different from that which obtains, for example, with oxygen-containing complexes of boron trifluoride [11] since the oxygen atom, unlike nitrogen, has a second lone pair of electrons available to solvate the proton. Finally, a 1 : 1 complex of hypothetical structure (III), which is essentially an anhydrous acid, would be far less stable than the corresponding 1 : 2 complex (IV) which is its pyridinium salt. The reverse is true, the 1 : 1 complex being the more stable. Reference to the complexes of boron trifluoride is again relevant for, in those systems which are known to furnish hydrogen ions, the 1 : 2 complexes are invariably the more stable.[11] For these reasons, structures (I)—(IV) cannot be accepted.

A structure (V) which accounts for the observed facts can be derived from the gallium trichloride dimer. The molten complex should be an ionic conductor, but hydrogen would not be evolved on electrolysis. Moreover, structure (V) explains the great similarity in properties of this complex and gallium trichloride–phosphorus oxychloride, $POCl_2^+GaCl_4^-$ (m. p. 118·5°, $\kappa = 1{\cdot}26 \times 10^{-3}$, $\mu = 0{\cdot}227$, $\mu\eta = 0{\cdot}442$, $E_\kappa = 4{\cdot}10$, $\eta = 1{\cdot}95$, $E_\eta = 3{\cdot}41$, $\Delta H_{vap} = 18$, etc.).[7] The presence of a large cation in both these complexes lowers the m. p. below that of other tetrachlorogallates such as $Ga^+GaCl_4^-$, m. p. 170°, and $K^+GaCl_4^-$, m. p. 259°.

An instructive analogy can also be drawn between the 1 : 1 complex $GaCl_3,C_5H_5N$ (m. p. 126°) and the corresponding complexes BCl_3,C_5H_5N (m. p. 115°) [12] and $AlCl_3,C_5H_5N$ (m. p. 118°).[13] Infrared data on the boron complex have been interpreted in terms of the structure $[py_2BCl_2]^+BCl_4^-$,[12] and an analogous formula $[py_2AlCl_2]^+AlCl_4^-$ would explain the observation [13] that the aluminium complex is dimeric in benzene but monomeric in nitrobenzene; clearly the ionic formulation suggested here would lead to an apparent molecular weight equal to that of monomeric $AlCl_3,C_5H_5N$ if ionic dissociation were complete, as it may well be in nitrobenzene (dielectric constant $\varepsilon = 35{\cdot}7$), whereas in a solvent of very low dielectric constant such as benzene ($\varepsilon = 2{\cdot}3$) association into ion pairs would lead to a molecular weight corresponding to the dimer $(AlCl_3,C_5H_5N)_2$.

The 1 : 2 complex between gallium trichloride and pyridine is most simply considered as the chloride corresponding to structure (V): $[py_2GaCl_2]^+Cl^-$. Thus, no hydrogen

[11] Greenwood and Martin, *Quart. Rev.*, 1954, **8**, 1.
[12] Greenwood, Wade, and Perkins, 16th Congress I.U.P.A.C. (Inorganic Section), Paris 1957, in the press.
[13] Eley and Watts, *J.*, 1952, 1914.

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would be expected on electrolysis as would be the case with structure (IV) and the lower stability of the complex could be related to the disparity in size of the cation and anion. An alternative structure for the 1 : 2 complex which cannot be eliminated on the present evidence is $[py_4GaCl_2]^+GaCl_4^-$, though this is perhaps less likely in view of the normal preference of gallium for tetrahedral rather than octahedral co-ordination. It is hoped to obtain more definite evidence on the nature of the ions present in these complexes by Raman spectroscopy and nuclear magnetic resonance. Thus, although the Raman spectrum of the cation $[py_2GaCl_2]^+$ is expected to be complicated, it may be possible to identify the four lines characteristic of $GaCl_4^-$ in the molten 1 : 1 complex. Similarly, if structure (V) is correct there are two chemically different types of gallium atom in the complex and these might be detected by studying the chemical shifts in the high-resolution nuclear magnetic resonance spectrum of gallium in the molten complex. By contrast, the suggested structure for the 1 : 2 complex does not contain the $GaCl_4^-$ ion and all the gallium atoms are in the same chemical environment.

The extent to which the 1 : 1 and 1 : 2 complexes are ionically dissociated into kinetically free units requires some discussion. From arguments previously outlined [14] the degree of ionic dissociation (α, %) should be given approximately by the expression

$$\alpha = 100\ M\kappa\eta/(2d\boldsymbol{N}\boldsymbol{e}v_0) = 50\ \mu\eta/(\boldsymbol{N}\boldsymbol{e}v_0)$$

In these expressions M is the monomeric molecular weight, κ the specific conductivity, η the dynamic viscosity (cP), d the density and v_0 an assumed average mobility of the ions in a medium having a viscosity of 1 cP. For moderately-sized ions, such a mobility is normally about 5×10^{-4} cm.^{2} sec.$^{-1}$ v^{-1} and if this and the numerical values of $\boldsymbol{N}$ and $\boldsymbol{e}$ are substituted then the quantity $50/(\boldsymbol{N}\boldsymbol{e}v_0)$ becomes (fortuitously) equal to unity, so that the percentage degree of dissociation is given directly by the reduced conductivity $\mu\eta$. In the case of the 1 : 1 compound $[py_2GaCl_2]^+GaCl_4^-$ it would be more appropriate to use the dimeric molecular weight for M so that $\alpha = 2\mu\eta$. On this basis, the complex would appear to be dissociated to the extent of about 2% into kinetically free ions, the corresponding figure for the 1 : 2 complex being about 5—8%.

Two observations should be made: (i) The calculated degree of ionic dissociation for the 1 : 1 complex is of the same order as that calculated for $POCl_2^+GaCl_4^-$.[7] On the other hand, the Raman spectrum of the molten phosphorus oxychloride complex can be interpreted in terms of complete (100%) ionization into $POCl_2^+GaCl_4^-$.[15] The distinction is between ionization and ionic dissociation and the difference in the two values may be due to ion-pair formation which would not influence the number of lines in the Raman spectrum but would reduce the number of kinetically free ions. A value of 2% for the ionic dissociation should therefore not be taken as necessarily implying that the remaining 98% of the complex is molecular; it may well be ionic as in the case of the phosphorus oxychloride complex. (ii) The calculation of the degree of ionic dissociation assumes that the ionic mobility is viscosity-controlled so that conductivity is exactly inversely proportional to viscosity. This is not the case for the 1 : 2 complex and, instead of E_η being equal to E_μ, the ratio E_η/E_μ is approximately 1·4, which is larger than that for any other complex studied. As a result, the value of $\mu\eta$ decreases with rise in temperature. This could be interpreted as arising from a change in the number of kinetically free ions with temperature (decrease in α) but it is not considered that the method of calculation is sufficiently refined to interpret this change in terms of equilibrium constants, free energies, and entropies of ionic dissociation as has recently been suggested.[16] An alternative and more plausible interpretation is that the mechanisms of conduction and viscosity, though similar, are not identical so that the ionic mobility is not entirely viscosity-controlled.

[14] Greenwood and Martin, *J.*, 1953, 1427.
[15] Woodward (Chem. Soc. Meeting at Cambridge, 1957), *Chem. Soc. Special. Publ.* No. 8, in the press.
[16] Bradley, *Trans. Faraday Soc.*, 1956, **52**, 1255.

The postulated ions for the 1 : 2 complex, $[py_2GaCl_2]^+$ and Cl^-, are very different in size. In such a situation, conduction may occur relatively easily by migration of the smaller ions through the interstices in the disordered network of the larger ions, whereas viscous flow involves the configurational breakdown or shear of the larger ions over each other. The activation energy of conduction would then be less than that of viscous flow, as observed for the 1 : 2 complex. A similar situation is well known for the alkali-metal halides where E_η remains approximately constant for a given halogen whilst E_μ, which is considerably smaller than E_η, increases from the lithium halide to the cæsium halide as the size of the cation increases.[17]

THE UNIVERSITY, NOTTINGHAM. [*Received, November 18th*, 1957.]

[17] Bloom and Heymann, *Proc. Roy. Soc.*, 1947, *A*, **188**, 392.

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331. *Addition Compounds of Gallium Trichloride. Part VI.*[1] *Complexes with Piperidine.*

By N. N. GREENWOOD and K. WADE.

The new addition compounds $GaCl_3,C_5H_{10}NH$ (m. p. 134°) and $GaCl_3,2C_5H_{10}NH$ (m. p. 112°) have been studied to determine what effect the removal of the aromatic character from pyridine has on the electron-donor properties of the ligand. The two piperidine complexes are very similar to the corresponding pyridine complexes though certain differences in detail appear, which can be ascribed to the buckling of the heterocyclic ring when saturated. The complexes are ionic and can be formulated as $[pip_2GaCl_2]^+GaCl_4^-$ and $[pip_2GaCl_2]^+Cl^-$.

PIPERIDINE differs from pyridine in at least three ways which might be expected to influence its properties as a ligand: (*a*) the absence of aromatic character, (*b*) the buckling of the ring, and (*c*) the presence of an *N*-hydrogen atom. The removal of aromatic character increases the electron density near the nitrogen atom and so increases the donor strength of the ligand; for example, piperidine forms a 1 : 1 addition compound with trimethyl borate $(MeO)_3B$ whereas pyridine does not,[2] and the heat of addition of piperidine to stronger electron acceptors such as boron trichloride or gallium trichloride is greater than that of pyridine.[3] However, in the case of a strong electron acceptor, moderate variations in the actual strength of the donor–acceptor bond may not alter the physical properties of the complexes appreciably provided that the temperature at which comparison is made is not so great as to dissociate the bond.

Ring buckling increases the steric requirements of the piperidine molecule and this may influence the stability of a complex if there are a considerable number of such ligands surrounding a very small acceptor atom. Where this is not so, the most likely effect of substituting piperidine for pyridine would be to increase those properties (such as molar volume and Batschinski's constant) which depend to some extent on molecular dimensions, and to influence those properties which depend, at least in part, on molecular symmetry (such as activation energy of viscous flow). These considerations clearly apply equally to the ligands themselves and it will be shown that the molar volume, Batschinski constant, and activation energy of viscous flow are all greater for piperidine than for pyridine.

The third difference between the two ligands is the presence of an *N*-hydrogen atom in piperidine. It is unlikely that hydrogen bonding would occur in the piperidine complexes since there is no evidence that it plays a significant part in modifying the properties of the

[1] Part V, Greenwood and Wade, preceding paper.
[2] Venkataramaraj, Urs, and Gould, *J. Amer. Chem. Soc.*, 1952, **74**, 2948.
[3] Greenwood, Wade, and Perkins, *16th Congress I.U.P.A.C.* (*Inorganic Section*), Paris 1957, in the press; Greenwood, Proc. Symposium on Coordination Chemistry, Rome, 1957, in the press.

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ligands themselves; for example, the b. p. and dynamic viscosity of piperidine are both less than, not greater than, those of pyridine. On the other hand, the mode of ionization of piperidine complexes might well be determined by the relative ease or difficulty of ionizing the N–H bond. Changes in the distribution of electronic charge following co-ordination involving the non-bonding electrons on the nitrogen atom should facilitate ionization of the proton, but energetically still more favourable ways of ionizing it might conceivably exist.

This work was undertaken to answer questions arising from speculations of this type. The 1 : 1 and the 1 : 2 complex of piperidine resemble the corresponding pyridine complexes very closely in many properties; this is ascribed to a similarity in their ionic structure. The absence of cathodic hydrogen on electrolysis eliminates the possibility of ionization's involving hydrogen ions and the complexes are best considered in terms of complex cations containing tetrahedrally co-ordinated gallium: $[pip_2GaCl_2]^+GaCl_4^-$ and $[pip_2GaCl_2]^+Cl^-$. On the basis of these structures a detailed interpretation of the similarities and differences between the complexes and those of pyridine is possible.

Experimental and Results

Preparation, purification, and methods were as in the preceding paper.[1] Piperidine (m. p. −4°, b. p. 106·3°) was dried (KOH or BaO) before being fractionated.

When successive amounts of piperidine were condensed on gallium trichloride in a vacuum line, the m. p. of the system varied as shown in Fig. 1, which also incorporates results obtained in the region 50—80 moles % of piperidine by evaporating this component out of the reaction vessel after the first set of readings had been taken. The two sets of results substantially agree, which implies that only piperidine is volatile over mixtures containing more piperidine than would correspond to the 1 : 1 complex. There were maxima at 50 moles % ($GaCl_3,C_5H_{10}NH$, m. p. 134°) and 66·7% ($GaCl_3,2C_5H_{10}NH$, m. p. 112°). The eutectics could not be obtained satisfactorily because of extensive supercooling but graphically they can be placed at about 28 moles % of piperidine (<0°), at 59% (~100°), and at about 90% (<−5°). As in the pyridine system, the flatter maximum of the 1 : 2 compound indicates that it was more dissociated in the liquid phase than was the 1 : 1 compound. In agreement with this, whereas the vapour pressure of the 1 : 1 complex was negligible below 160°, the 1 : 2 complex had a vapour pressure of about 13 mm. Hg at room temperature (cf. 20—25 mm. for piperidine itself).

The 1 : 1 *Complex*, $GaCl_3,C_5H_{10}NH$.—The specific electrical conductivity was measured at 1000 cycles/sec. on a specimen purified as usual by successive fractional freezings under vacuum in an apparatus sealed directly to the conductivity cell. A conductivity–temperature run between the m. p. (134°) and 174° showed that the complex decomposed slowly above 150°; for example, the specific conductivity increased by 2% during 2 hr. at 151° and by 10% in 3 hr. at 170°. A second run on this now slightly modified sample gave results which were quite reproducible between 128° and 143° but were about 14% higher than those for the compound when originally sealed in the cell. The results of this second run are given in Table 1 which indicates the sequence of measurements; the duration of the run was 12 hr. At the m. p. the specific conductivity, κ, is $1·969 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$, the molar conductivity, μ, is 0·346 cm.^{2} ohm^{-1} mole^{-1}, and the reduced conductivity, $\mu\eta$, is 1·63 cm.^{2} cP ohm^{-1} mole^{-1}. The specific conductivity of the sample when first melted was $1·70 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$ at the m. p.

The figures in Table 1 lead to a temperature coefficient which is probably quite accurate, since it agrees with the coefficient calculated from the few reliable low-temperature readings obtained on the first run. The plots of log μ (Fig. 2) and log κ against $1/T°(\text{K})$ are linear throughout the range; $E_\kappa = 5·61$ kcal. mole^{-1}, $E_\mu = 5·87$ kcal. mole^{-1}.

D.C. current–voltage curves at 139° indicated a decomposition potential of 0·58 v for the molten 1 : 1 complex and this low value was confirmed in a back-e.m.f. experiment in which the maximum value was 0·5 v. No gas was evolved during electrolysis between bright platinum electrodes but a charred deposit was observed streaming down from the anode. After 15 minutes' electrolysis at 2—4 mA the anode was covered with a black deposit and the cathode had turned dull. The A.C. resistance of the cell was virtually unchanged after the D.C. experiment.

The viscosity of a carefully purified sample of gallium trichloride–piperidine was measured in a sealed, weir-type viscometer between 122° and 160°. Measurements, taken on four successive days (Table 2), indicate both the reproducibility of the measurements and the stability of the complex insofar as it affects the viscosity. Efflux times varied between 100

FIG. 1. *Phase diagram of the system* $GaCl_3$–$C_5H_{10}NH$.

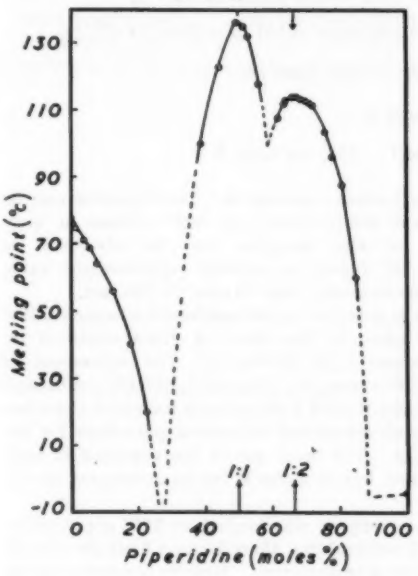

FIG. 2. *Properties of molten* $GaCl_3,C_5H_{10}NH$.

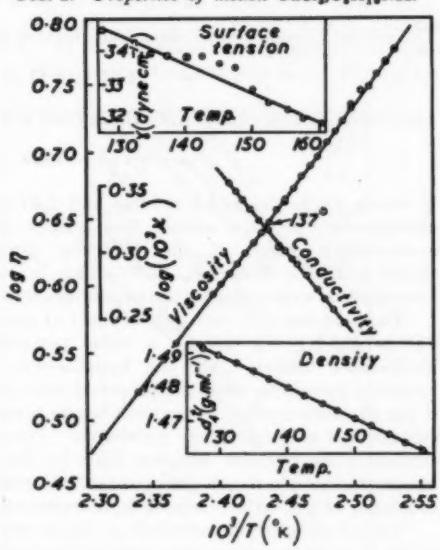

TABLE 1. *Electrical conductivity of* $GaCl_3,C_5H_{10}NH$ *between* 128° *and* 143°.

No.	Temp.	$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{3} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{3} cP ohm^{-1} mole^{-1})	No.	Temp.	$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{3} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{3} cP ohm^{-1} mole^{-1})
4	128·0°	1·770	0·3099	1·640	1	136·1°	2·037	0·3586	1·622
5	129·3	1·810	0·3174	1·639	17	136·1	2·043	0·3596	1·627
6	130·2	1·841	0·3228	1·638	10	137·2	2·075	0·3656	1·619
7	131·2	1·872	0·3285	1·627	11	138·3	2·112	0·3722	1·619
2	132·5	1·916	0·3365	1·632	12	139·3	2·148	0·3789	1·619
8	133·7	1·954	0·3435	1·629	13	140·3	2·185	0·3857	1·619
3	134·1	1·974	0·3470	1·632	14	141·2	2·217	0·3914	1·617
9	135·1	2·002	0·3522	1·629	15	142·1	2·251	0·3978	1·617
					16	143·2	2·292	0·4052	1·617

TABLE 2. *Viscosity of* $GaCl_3,C_5H_{10}NH$ *between* 122° *and* 159°.

Supercooled			Molten			Supercooled			Molten		
Temp.	ν (cs)	η (cP)	Temp.	ν (cs)	η (cP)	Temp.	ν (cs)	η (cP)	Temp.	ν (cs)	η (cP)
121·9°	3·997	5·984	129·0°	3·483	5·192	135·0°	3·104	4·608	142·1°	2·749	4·065
122·9	3·911	5·851	130·0	3·423	5·099	136·1	3·060	4·540	143·2	2·701	3·990
123·9	3·827	5·722	131·0	3·339	4·970	137·1	2·994	4·439	144·2	2·656	3·920
124·9	3·762	5·622	132·1	3·291	4·896	138·1	2·947	4·366	149·2	2·454	3·611
125·9	3·689	5·508	133·0	3·231	4·803	139·1	2·894	4·286	154·2	2·268	3·327
126·9	3·612	5·389	134·0	3·172	4·713	140·1	2·847	4·213	159·2	2·108	3·081
127·9	3·547	5·290				141·1	2·797	4·136			

and 200 sec. and correspond, at the m. p., to a dynamic viscosity of 4·71$_3$ cP. The plot of log η against $1/T$(°K) given in Fig. 2 is probably better fitted by a smooth curve rather than by two straight lines, although there seems to be a region of maximum curvature at about 137°. The activation energy E_η decreases from 6·28 kcal. mole^{-1} at low temperatures to 5·84 kcal. mole^{-1}

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at the higher temperatures. The activation energy for viscous flow of the complex above its m. p. is therefore almost identical with the activation energy for molar conduction (E_μ = 5·87 kcal. mole^{-1}), so that the product $\mu\eta$ remains virtually constant above this temperature.

The density and surface tension between 127° and 161° are also plotted in Fig. 2. The density can be represented (±0·0001) by

$$d_4^t = 1{\cdot}4847 - 9{\cdot}38 \times 10^{-4}(t - 135) \text{ g. ml.}^{-1}$$

The surface tension results show some scatter but can be represented to within ±1·5% by

$$\gamma = 34{\cdot}05 - 8{\cdot}47 \times 10^{-2}(t - 135) \text{ dyne cm.}^{-1}$$

The corresponding equation for the surface free energy is

$$\omega = \gamma V_M^{\frac{1}{3}} = 1069 - 2{\cdot}34(t - 135) \text{ erg mole}^{-\frac{1}{3}}$$

in which V_M is the molar volume and 2·34 is the Eötvös constant k. The equation can be extrapolated to zero surface free energy (critical temperature) at 592° whence a very approximate value of the "boiling point" of the complex can be obtained as $\{\frac{8}{5}(592 + 273) - 273\}$, *i.e.*, 305°. This is some 70° below an equally approximate value estimated by extrapolating the vapour-pressure measurements from 13 mm. to 760 mm.

The parachor ($[P] = V_M\gamma^{\frac{1}{4}}$) of the 1 : 1 complex is constant in the temperature range studied and is 425·2 ± 0·8 (r.m.s.), a value remarkably close to the value of 424·4 obtained by McGowan's method [4] for the hypothetical structure $C_5H_{11}N\rightarrow GaCl_3$. The agreement is probably fortuitous since the proposed structure of the complex, $[pip_2GaCl_2]^+GaCl_4^-$, although it has the same number of covalent bonds, is essentially that of a molten salt for which parachor calculations are notoriously unreliable. Thus, the observed and calculated parachors for the corresponding pyridine complex differ by 20·1 units. The main use of the parachor in such circumstances is not as a guide to molecular structure, but as a check, by its constancy, on the reliability of the surface-tension measurements.

Vapour-pressure experiments in which the 1 : 1 complex was heated to 245° appeared to result in slight decomposition with the formation of residual gas, there being a final pressure of 3·0 mm. in the apparatus at room temperature after a typical run. Results obtained during 5 hr. on a freshly recrystallized sample of complex, which had been degassed under vacuum by short immersion in a bath at 170°, are listed in Table 3. They correspond to the equation

$$\log p \text{ (mm.)} = 9{\cdot}811 - 4486/T$$

which leads to a latent heat of evaporation, ΔH_{vap}, of 20·5$_3$ kcal. mole^{-1}. The ratio $\Delta H_{vap}/E_\eta$ has the reasonable value 3·52.

TABLE 3. *Vapour pressure of molten* $GaCl_3,C_5H_{10}NH$ *between* 159° *and* 242°.

Temp.	159·3°	176·0°	184·2°	193·8°	202·4°	211·1°	220·0°	232·0°	242·1°
p (mm. Hg)	(0·01)	0·51	1·01	1·63	2·42	3·51	5·23	8·26	12·84

The 1 : 2 *Complex* $GaCl_3,2C_5H_{10}NH$.—The complex (m. p. 112°) was synthesized to within 1 part in 10^4 (w/w) by condensing 6·0497 g. of freshly fractionated piperidine on 6·2556 g. of gallium trichloride in a vacuum line. Because of the high vapour pressure of piperidine above the complex the compound could not be purified by fractional crystallization but care was taken in all manipulations to transfer the complex quantitatively *in vacuo*. Thus, the conductivity cell was fitted with a receiving limb into which the compound was sealed after the measurements had been made and this was in turn sealed into the viscometer unit (which in this instance did not incorporate a glass sinter for vacuum filtration because of the risk of losing piperidine from the melt). The volumes were such that even if the pressure above the 1 : 2 complex reached 1 atm. the change in composition of the liquid phase would be less than 1 mole % of piperidine in the conductivity experiments and about 3 moles % in the viscosity measurements.

The conductivity of molten gallium trichloride–dipiperidine between 105° and 138° is listed

[4] McGowan, *Rec. Trav. chim.*, 1956, **75**, 193.

in Table 4 and plotted logarithmically in Fig. 3. There was no pronounced drift at any temperature but the check-reading at 123·9° showed that the conductivity had increased by 0·38% during 2½ hr. This slight decomposition was confirmed on a second sample which gave readings some 3% higher than those obtained on the first run after having been deliberately heated for about 1 hr. at 145°. However, such variations should in no way invalidate the main conclusions to be drawn from the investigation (see Discussion). For comparison with the 1 : 1 compound, the value of the specific conductivity, κ, at 134° can be calculated to be $1{\cdot}279 \times 10^{-3}$ ohm^{-1} cm.$^{-1}$ which corresponds to a molar conductivity, μ, of 0·340 cm.^{2} ohm^{-1} mole^{-1} and a reduced conductivity, $\mu\eta$, of 1·37 cm.^{2} cP ohm^{-1} mole^{-1}. At this temperature, therefore, the conductivities of the two complexes are very similar, those of the 1 : 2 complex being slightly the

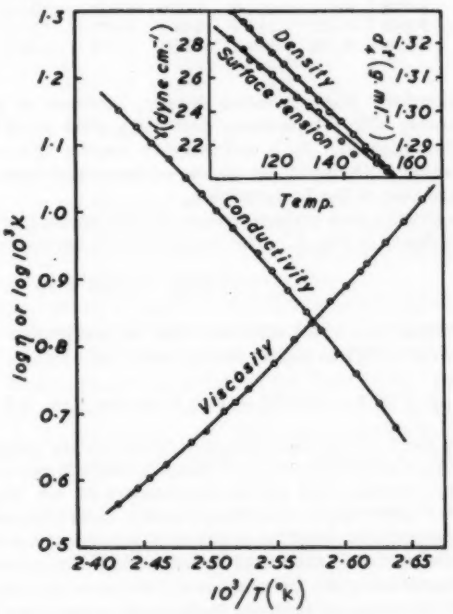


FIG. 3. *Properties of molten* $GaCl_3.2C_5H_{10}NH$.

smaller. This difference is emphasized if comparison is made at the respective melting points, but even then the reduced conductivities of the two complexes remain similar.

The activation energy of conduction, E_κ, varied from 11·79 kcal. mole^{-1} at lower temperatures to 9·12 kcal. mole^{-1} at the higher temperatures. Corresponding values for E_η are 11·90

TABLE 4. *Electrical conductivity of* $GaCl_3.2C_5H_{10}NH$ *between* 106° *and* 138°.

No.	Temp.	$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{2} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{2} cP ohm^{-1} mole^{-1})	No.	Temp.	$10^3\kappa$ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{2} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{2} cP ohm^{-1} mole^{-1})
17	105·8°	0·4789	0·1246	1·169	8	123·9°	0·9485	0·2504	1·301
16	107·7	0·5205	0·1356	1·185	18*	123·9	0·9521	0·2511	1·304
15	110·1	0·5750	0·1501	1·211	7	125·8	1·008	0·2663	1·321
14	111·9	0·6172	0·1613	1·225	6	127·7	1·069	0·2828	1·333
13	113·9	0·6663	0·1744	1·239	5	129·7	1·127	0·2986	1·336
12	115·6	0·7117	0·1865	1·251	4	131·7	1·202	0·3193	1·363
11	117·6	0·7674	0·2015	1·277	3	133·8	1·272	0·3380	1·369
10	119·4	0·8189	0·2152	1·282	2	135·7	1·341	0·3572	1·382
9	121·6	0·8810	0·2320	1·291	1	137·8	1·419	0·3784	1·398

* After 5 hr. at various temperatures.

and 9·70 kcal. mole^{-1} respectively. These high values, which are paralleled by high values for E_η, are nearly twice as great as the figures obtained for the 1 : 1 complex. A similar effect

was noted for the viscosity of the two pyridine complexes of gallium trichloride, though in these the difference in activation energies of conduction was not so great.

The results of a viscosity run on the 1 : 2 complex between 102° and 138° are presented in Table 5 and Fig. 3. Readings were taken on three successive days. At 134° (the m. p. of the 1 : 1 compound) the dynamic viscosity, η, is 4·03 cP which is similar to the viscosity of the

TABLE 5. *Viscosity of* $GaCl_3,2C_5H_{10}NH$ *between* 102° *and* 138°.

Temp.	ν (cs)	η (cP)	Temp.	ν (cs)	η (cP)	Temp.	ν (cs)	η (cP)	Temp.	ν (cs)	η (cP)
102·9°	7·839	10·463	111·1°	5·865	7·779	122·2°	4·154	5·461	132·2°	3·234	4·220
104·9	7·264	9·680	112·9	5·559	7·362	123·7	3·980	5·227	134·1	3·083	4·016
106·9	6·773	9·012	114·9	5·170	6·837	125·1	3·852	5·053	135·6	2·981	3·878
108·9	6·340	8·422	116·9	4·901	6·471	127·3	3·596	4·710	138·1	2·827	3·670
109·6	6·170	8·193	119·3	4·535	5·977	129·1	3·468	4·535			

1 : 1 complex. The activation energy, however, is greater, as just mentioned, and varies considerably with temperature, decreasing from 10·08 to 7·65 kcal. mole^{-1} in the temperature range investigated. It is not easy to ascribe this variation predominantly to changes in composition of the melt due to loss of piperidine since the viscosity of the 1 : 1 complex is so similar to that of the 1 : 2 complex.

The density and surface tension of gallium trichloride–dipiperidine between 105° and 155° are also shown in Fig. 3. The density can be expressed to within 0·05% by the equation

$$d_4^t = 1{\cdot}3253 - 1{\cdot}026 \times 10^{-3}(t - 112) \text{ g. ml.}^{-1}$$

Similar equations which reproduce the surface tension to within 0·2 dyne cm.$^{-1}$ and the molar surface free energy to within 20 erg mole$^{-\frac{1}{3}}$ are

$$\gamma = 27{\cdot}3 - 0{\cdot}167(t - 112) \text{ dyne cm.}^{-1}; \quad \omega = 1123 - 6{\cdot}56\ (t - 112) \text{ erg mole}^{-\frac{1}{3}}$$

As with the 1 : 2 pyridine complex, these surface properties are sensitive to slight changes in composition at the interface and this may explain the anomalously large temperature coefficient of surface tension and Eötvös constant (6·56 erg deg.$^{-1}$ mole$^{-\frac{1}{3}}$). This explanation is also consistent with the parachor values which, unlike those of the nonvolatile 1 : 1 complexes which were constant, decreased from 600 to 575 as the temperature rose from 105° to 155°. It is not profitable to modify this trend by using the full parachor formula $[P] = \gamma^{\frac{1}{4}}M/(d_{\text{liq}} - d_{\text{gas}})$ since the composition of the gas phase is not the same as that of the liquid. Moreover, simple application of the extended formula, made on the assumption that the vapour above the liquid phase is, in fact, the 1 : 2 complex, shows that an increase in vapour pressure of the order of 2 atm. would be required to account for the observed drop in parachor over the temperature range of 50°. Change in composition of the surface is thus the more probable explanation.

DISCUSSION

From a comparison of corresponding properties it is at once apparent that the complexes of gallium trichloride with pyridine and piperidine are closely similar, any differences being of detail rather than of kind. The arguments of the preceding paper, applied to the present compounds, lead to the formulæ $[pip_2GaCl_2]^+GaCl_4^-$ and $[pip_2GaCl_2]^+Cl^-$ and are based on the following main lines of evidence: (i) The 1 : 1 complex can add a further mol. of ligand to give the 1 : 2 complex; (ii) both complexes are good electrical conductors when molten (Table 6); (iii) the properties of the 1 : 2 complex are similar to those of the 1 : 1 complex except that it dissociates more readily; and (iv) electrolysis does not result in cathodic evolution of hydrogen. Similarly, the extent to which the compounds are dissociated into kinetically free ions can be estimated if the standard ionic mobility used for the pyridine complexes [1] is adopted for the piperidine complexes also. The degree of dissociation (α) of the 1 : 1 complexes is then given by $2\mu\eta$ and is about 2% for $GaCl_3$,py

and about 3% for $GaCl_3$,pip; the value for the 1 : 2 complexes is given by $\mu\eta$ directly and is about 6% for $GaCl_3$,2py and about 1% for $GaCl_3$,2pip. These estimates should be correct to within a factor of 2 or 3.[5] Reference to Table 6 shows that the values of α for the complexes are far greater than those for gallium trichloride and the ligands themselves which are virtually un-ionized. It is also noteworthy that the degree of ionic dissociation of the complexes is practically independent of both the ligand and the combining ratio

TABLE 6. *Comparison of some conduction and viscosity characteristics.*

Compound	M. p.	$10^2\kappa_{120}$	$(\mu\eta)_{120}$	η_{120}	E_μ	E_η	10^3B
Ga_2Cl_6	77·8°	0·002	$3·6 \times 10^{-4}$	1·038	(~1)	3·64	5·75
Pyridine	−41·8	<0·001	$\sim 10^{-5}$	0·339	—	2·67	6·43
Piperidine	−10·5	<0·001	$\sim 10^{-4}$	0·283	—	3·82	8·50
$GaCl_3$,py	126	2·50	1·07	2·626	4·39	3·96	7·63
$GaCl_3$,2py	113	10·89	6·28	2·332	4·21	7·80	7·03
$GaCl_3$,pip	134	1·50	1·65	6·240	5·87	5·84	10·6
$GaCl_3$,2pip	112	0·836	1·28	5·852	11·9	10·1	14·6

and varies little with temperature. The values can not yet be discussed in more detail because of the approximate nature of the calculations and the uncertain interpretation of the calculated degrees of dissociation not being nearer 100%. Two further topics, however, arise from Table 6: (*a*) the viscosity of the complexes, their activation energies, and Batschinski constants; and (*b*) the similarity in m. p. of the complexes.

The dynamic viscosities of the complexes of gallium trichloride with pyridine and piperidine are all greater than the viscosities of their components. For example, the results in Table 6 show that, at the arbitrarily chosen temperature of 120°, the viscosity of the pyridine complexes is about 7 times greater than that of pyridine itself; the factor for the piperidine complexes is about 21. Moreover, the viscosity of the 1 : 2 complexes is less than that of the corresponding 1 : 1 compounds; in this the complexes resemble those of boron trifluoride for which also the viscosity of the 1 : 1 complex is always the greater.[6]

The activation energy, E_η, is also increased by co-ordination in agreement with the ionic nature of the complexes. Thus, in general, activation energies of viscous flow for molecular liquids (including non-polar, polar, hydroxylated, and hydrogen-bonded liquids) are small and fall in the range 0·4—4 kcal. mole^{-1} whereas those for highly ionized molten salts (such as the alkali halides) fall mainly in the range 4—10 kcal. mole^{-1}.[7] Table 6 indicates that the present donors, acceptor, and complexes conform to this classification. It is also seen that the activation energies for piperidine and its complexes are larger than those of pyridine and its complexes respectively; this seems reasonable in view of the piperidine molecule's being far less symmetrical than the planar pyridine molecule owing to the buckling effect of its tetrahedral carbon bond angles. It may also be significant that the 1 : 2 complexes have higher activation energies than those of the 1 : 1 complexes. At first sight this may seem surprising, as the 1 : 2 complexes contain a greater proportion of the ligands (L) which have low activation energies. However, activation energies should be roughly inversely proportional to the sum of the ionic radii since the larger the ions the more nearly do they approach a molecular, non-ionic configuration and the smaller the influence of the unit charges. The effect is therefore understandable in terms of the suggested structures, as the 1 : 1 complexes involve two moderately large ions, $[L_2GaCl_2]^+GaCl_4^-$, whereas the 1 : 2 complexes involve only one, $[L_2GaCl_2]^+Cl^-$.

Values of Batschinski's constant B (ml. cP g.$^{-1}$)are tabulated in the last column of Table 6. The constant, which is a rough guide to the size of the flow units in a liquid, can be obtained from the relation $\eta = B/(v - b)$ in which v is the specific volume and b a

[5] Greenwood and Martin, *J.*, 1953, 1427.
[6] *Idem*, *Quart. Rev.*, 1954, **8**, 1.
[7] Ward, *Trans. Faraday Soc.*, 1937, **33**, 88.

constant. The equation implies a linear relation between specific volume and fluidity, $v = b + B\phi$, and this holds to a fair degree of approximation for the 1 : 1 complexes above their m. p.s. Deviations from linearity are more marked for the 1 : 2 complexes, the slope decreasing with rise in temperature. The values listed in Table 6 can be interpreted as follows: (*a*) the value for piperidine is greater than that for pyridine because of the greater steric requirements of the buckled ring. The values for the piperidine complexes are greater than those for the pyridine complexes for the same reason; (*b*) complex formation increases the value of *B*. Thus, the values for the pyridine complexes are greater than those for either pyridine or gallium trichloride alone and the same is true for the piperidine complexes. This is consistent with the presence of large ions such as $[L_2GaCl_2]^+$ but does not prove their existence since an increase would also be expected for simple molecular addition compounds of the type $L \rightarrow GaCl_3$; (*c*) the Batschinski constant for the 1 : 2 pyridine complex is *smaller* than that for the 1 : 1 complex. The same is true for certain complexes of boron trifluoride (*e.g.*, the hydrates [8]) and in each case the values are consistent with the relative sizes of the postulated ions. For example, both pyridine complexes contain the same cation, $[py_2GaCl_2]^+$, but the anion of the 1 : 2 complex, Cl^- is *smaller* than that of the 1 : 1 complex, $GaCl_4^-$. Similarly both hydrates contain the same anion, $[BF_3{\cdot}OH]^-$, but the cation of the 1 : 2 complex, H_3O^+, is *smaller* than that of the 1 : 1 complex, $[H_3O{\cdot}BF_3]^+$. The piperidine complexes do not conform to these considerations, the value of *B* for the 1 : 2 complex being larger than that for the 1 : 1 complex despite the fact that the postulated anion is smaller. Such reversals in the relative values of Batschinski's constant are not unknown [9] and emphasize the care which must be taken in drawing detailed conclusions about molecular structure from the bulk properties of compounds.

The similarity in m. p. observed for the four complexes of gallium trichloride with pyridine and piperidine is not confined to these complexes alone but is part of a curious and hitherto unexplained tendency shown by a variety of complexes between electron-deficient halides and various ligands.[10] This is illustrated in Table 7: the m. p.s of the 19 complexes all fall within a range of 14° whereas the m. p.s of the constituent donor and acceptor moieties are spread evenly over a range of 326°. Many other examples could be chosen and, although exceptions such as the complex BCl_3,pip which melts at 184° are also known, yet it remains true that an extraordinary number of complexes melt between 100° and 150°. This is hard to understand if the complexes are considered as covalent molecules (because of the wide variation in molecular weight) but is quite consistent with their formulation as ionic compounds. The fact that their m. p.s are lower than those of many molten salts is ascribed to the presence of large ions, the greater interionic distances reducing the Coulomb attractive force and hence lowering the m. p. It is significant that the m. p.s of many substituted ammonium picrates fall within the same range, *e.g.*, Pr^n_3NHPic, m. p. 114°, Pr^n_4NPic, m. p. 119°, and n-$C_7H_{15}NH_3Pic$, m. p. 124°. These compounds by their nature must be ionic and, moreover, they have similar conduction characteristics to those of the present complexes.[5]

If the explanation advanced in the preceding paragraph to account for the similarities in the m. p.s of complexes is correct, then it follows that all the complexes listed in Table 7 are ionic. The aluminium halide complexes with ammonia and pyridine have previously been considered as molecular [10] despite the fact that, in those cases where the electrical conductivity of the molten complexes has been studied,[11] the molar conductivities were very similar to those of the complexes of gallium trichloride investigated here. The confusion appears to have arisen because the estimated degree of ionic dissociation of the

[8] Greenwood, *J. Inorg. Nuclear Chem.*, 1958, **5**, 224, 229.
[9] Greenwood and Worrall, *ibid.*, in the press.
[10] Klemm and Tanke, *Z. anorg. Chem.*, 1931, **200**, 343; Klemm, Tilk, and Jacobi, *ibid.*, 1932, **207**, 187; Eley and Watts, *J.*, 1952, 1914.
[11] Klemm, Clausen, and Jacobi, *Z. anorg. Chem.*, 1931, **200**, 367.

ammines was of the order of 1%; the rest of the structure was considered to comprise covalent molecules rather than ion pairs as in the present interpretation. Again, the Raman spectrum of the molten complex $AlCl_3,NH_3$, which consists of 20 lines, has been interpreted in terms of an " ethane-like " molecular structure $H_3N,AlCl_3$.[12] This structure would be expected to give 12 lines, as observed for example in the isoelectronic compound methyltrichlorosilane, $H_3C{\cdot}SiCl_3$. The discrepancy was qualitatively ascribed to an assumed distortion of the structure which reduced the symmetry and hence increased the number of lines. As against this, the ionic structure now suggested, *viz.*, $[(NH_3)_2AlCl_2]^+AlCl_4^-$, should give a spectrum of 20 lines, as observed, since it can be

TABLE 7. *Melting points of some complexes and their parent compounds.*

M. p. 112—115°	M. p. 117—120°	M. p. 124—126°	Ligands		Acceptors	
BCl_3,py	$AlCl_3$,py	$AlCl_3,NH_3$	NH_3	− 78°	BCl_3	−107°
$AlBr_3$,dioxan	$AlBr_3$,py	$AlBr_3,NH_3$	py	− 42°	$AlCl_3$	193°
AlI_3,py	$AlBr_3,PH_3$	AlI_3,NH_3	pip	− 11°	$AlBr_3$	97°
$GaCl_3$,2py	AlI_3,PH_3	$GaCl_3,NH_3$	PH_3	−133°	AlI_3	191°
$GaCl_3$,2pip	$GaCl_3,POCl_3$	$GaBr_3,NH_3$	Dioxan	12°	$GaCl_3$	78°
$GaBr_3,POCl_3$ *	$GaCl_3,Ph_3CCl$ *	$GaCl_3$,py	$POCl_3$	1°	$GaBr_3$	122°
		$GaBr_3$,py *	Ph_3CCl	112°		

* Unpublished observations in this laboratory.

considered as the sum of two spectra similar to those of the isoelectronic species $(CH_3)_2SiCl_2$ (16 lines) and $SiCl_4$ (4 lines). Whilst it is realized that mere enumeration of lines without a detailed study of their position, intensity, and polarization affords no proof of the structure, it does suggest that the reported assignments for this compound might profitably be reinvestigated.

There is no suggestion that all complexes of the Group III halides and related compounds have structures similar to those now proposed. Other structures are well known;[6] for example, the complexes of boron trifluoride with ammonia and pyridine have been shown by *X*-ray analysis to have the structures H_3N,BF_3 [13] and py,BF_3.[14] However, these compounds have widely differing m. p.s and stabilities [H_3N,BF_3, m. p. 163° (decomp.) [15]; py,BF_3, m. p. 48° [6], b. p. 300° [16]] and appear to differ also from the compounds listed in Table 7 in their electrochemical properties, where these have been investigated. For example, boron trifluoride–pyridine, which is ionically dissociated to a small extent when molten, evolves hydrogen at the cathode on electrolysis whereas boron trichloride–pyridine does not. Such differences will be discussed more fully later.

The authors of this and the preceding paper thank the Chemical Society for a grant from the Research Fund and the D.S.I.R. for a Maintenance Grant (to K. W.).

THE UNIVERSITY, NOTTINGHAM. [*Received, November 18th*, 1957.]

[12] Goubeau and Siebert, *Z. anorg. Chem.*, 1947, **254**, 126.
[13] Hoard, Geller, and Cashin, *Acta Cryst.*, 1951, **4**, 396; Hoard, Geller, and Owen, *ibid.*, p. 405.
[14] Zvonkova, *Kristallografiya*, 1956, **1**, 73.
[15] Laubengayer and Condike, *J. Amer. Chem. Soc.*, 1948, **70**, 2274.
[16] van der Meulen and Heller, *ibid.*, 1932, **54**, 4404.

XUM

332. *Electrical Conduction in Fused Gallium Dichloride and Gallium Dibromide.*

By N. N. Greenwood and I. J. Worrall.

Fused gallium dichloride and dibromide are typical molten salts. The variation of their conductivity and viscosity with temperature is characteristic of compounds in which the cation is considerably smaller than the anion. These results are consistent with recent structural investigations [1, 2, 3] which have shown the compounds to be $Ga^{+}[Ga^{III}Cl_4]^{-}$ and $Ga^{+}[Ga^{III}Br_4]^{-}$. The effect on the conductivity of adding excess of gallium to the dichloride was also studied. In addition, the density of pure gallium dichloride and dibromide and the surface tension of the dichloride have been determined over a range of temperature.

X-Ray crystal structure analysis [2] has shown that gallium dichloride is ionic, $Ga^{+}[GaCl_4]^{-}$, and the Raman spectrum of the fused compound indicates that this structure persists in the liquid state.[1] Gallium is therefore present equally in the oxidation states +1 and +3, consistent with the diamagnetism of the solid.[4] The diamagnetism of solid gallium dibromide and the Raman spectrum of the fused compound likewise indicate an ionic formulation $Ga^{+}[GaBr_4]^{-}$,[3] and, in the absence of more specific evidence, a similar structure may be presumed for the di-iodide on the grounds of its diamagnetism and the similarity in m. p. of the three compounds.[5] The dihalides can therefore be considered as addition compounds of the trihalides in which the unstable monohalides act as ligand, $GaX \rightarrow GaX_3$. Indeed, they constitute an unusual example of stabilization of an oxidation state by co-ordination for, in this instance, the complex ion (GaX_4^{-}) involves the normal valency state of the gallium atom whilst the less common +1 state is left unco-ordinated. Other examples of this phenomenon occur [6] in $Ga^{+}[AlCl_4]^{-}$ and $Bi^{+}[AlCl_4]^{-}$.

The importance of the dihalides in a study of the complexes of gallium trihalides lies in their unambiguously established structure and the fact that they should behave as molten salts despite their low m. p.s. Instructive comparisons can thus be made between the dihalides and addition compounds such as $POCl_2^{+}GaCl_4^{-}$ [7] and $POBr_2^{+}GaBr_4^{-}$,[8] the differences between the two sets of compounds residing in the size and electropositivity of the cations. Similarly, the properties of the complexes which the trihalides form with pyridine and piperidine have been interpreted on the basis of the structures $[py_2GaX_2]^{+}GaX_4^{-}$ [9,10] and $[pip_2GaX_2]^{+}GaX_4^{-}$ [10,11] in which the cations are even larger.

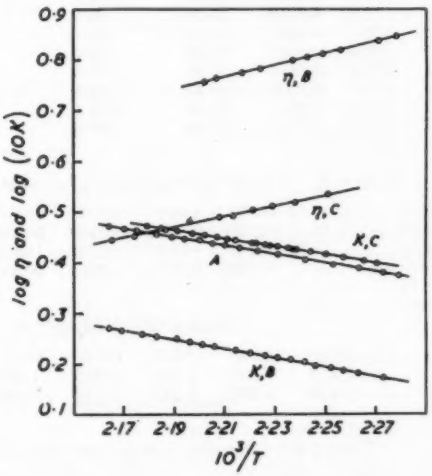
This investigation concerns the electrical conductivity and related properties of gallium dichloride and dibromide. The less stable di-iodide was not investigated. The compounds are true molten salts; the reduced conductivity indicates that they are completely dissociated into ions, and the variation of conductivity and viscosity with temperature is characteristic of compounds in which the cation is smaller than the anion. These properties are compared with those of silver nitrate as an analogous molten salt and with those of the previously mentioned co-ordination compounds of the gallium trihalides. Some results on gallium dibromide have already been summarized.[3]

[1] Woodward, Garton, and Roberts, *J.*, 1956, 3723.
[2] Garton and Powell, *J. Inorg. Nuclear Chem.*, 1957, **4**, 84.
[3] Woodward, Greenwood, Hall, and Worrall, *J.*, 1958, 1505.
[4] Klemm and Tilk, *Z. anorg. Chem.*, 1932, **207**, 175.
[5] Corbett and McMullan, *J. Amer. Chem. Soc.*, 1955, **77**, 4217.
[6] *Idem, ibid.*, 1956, **78**, 2906.
[7] Greenwood and Wade, *J.*, 1957, 1516.
[8] Greenwood and Worrall, *J. Inorg. Nuclear Chem.*, 1958, **6**, 34.
[9] Greenwood and Wade, *J.*, 1958, 1663.
[10] Greenwood and Worrall, unpublished observations.
[11] Greenwood and Wade, preceding paper.

XUM

Experimental and Results

Gallium dichloride was prepared by heating the trichloride [12] with slightly less than the stoicheiometric amount of gallium and then volatilizing the excess of trichloride from the molten mixture, and was purified by fractional freezing to constant m. p. 172·4°. The solid was pure white. Preparations in which there was an excess of gallium had lower m. p.s (169—170°); they were quite colourless and transparent when fused but were grey and opaque as solids. Literature values for the m. p. of the dichloride are 164°,[13] 165°,[1] and 170° ± 0·5°; [14] descriptions of these preparations indicate that the first contained excess of gallium and that the other two were contaminated with traces of the trichloride, which cannot be completely removed by volatilization.



Conductivity and viscosity of $Ga^+GaBr_4^-$ *(B) and* Ga^+GaCl^- *(C), with (A), κ for a solution of gallium in* $Ga^+GaCl_4^-$.

The preparation and purification of gallium dibromide (m. p. 166·7°) have been described.[3] The techniques used to measure conductivity, viscosity, density, and surface tension are as in earlier work.[9]

Gallium Dichloride, $Ga^+[GaCl_4]^-$.—The specific conductivity of fused gallium dichloride near its m. p. is given in Table 1. The results were reproducible during several hours and can be represented by the equation (see Fig.)

$$\log \kappa = 1{\cdot}180 - 784/T$$

This implies an activation energy, E_κ, of 3·59 kcal. mole^{-1}. Values of the molar conductivity, μ, calculated on the basis of the " dimeric " formula weight $Ga[GaCl_4]$, are also listed in Table 1 and lead to an activation energy, E_μ, of 3·81 kcal. mole^{-1}. This, as expected,[15] is larger than E_κ by an amount $RT^2\alpha$ where α is the coefficient of thermal expansion. At the m. p. (172·4°) the specific conductivity is $0{\cdot}264_2$ ohm^{-1} cm.$^{-1}$, the molar conductivity $30{\cdot}7_6$ cm.^{3} ohm^{-1} mole^{-1}, and the reduced conductivity (which compensates for the influence of viscosity on ionic mobility) 103·3 cm.^{3} cP ohm^{-1} mole^{-1}. The significance of these values is discussed later.

The effect of dissolved gallium metal on the conductivity of the dichloride was studied by heating pure gallium dichloride with excess of gallium at 180° for several hours and then transferring the clear solution into the same conductivity cell as was used for the preceding measurements. Under these conditions about 2 moles % of gallium is dissolved in the fused state [16] but this precipitates as an opaque grey dispersion in the solid state.[13] The process is reversible and the m. p. of the solid was 169°. Results are presented in Table 2 and the Figure

[12] *Idem, J.*, 1956, 1527.
[13] Lecoq de Boisbaudran, *Compt. rend.*, 1881, **93**, 294.
[14] Laubengayer and Schirmer, *J. Amer. Chem. Soc.*, 1940, **62**, 1578.
[15] Martin, *J.*, 1954, 3246.
[16] Corbett and von Winbush, *J. Amer. Chem. Soc.*, 1955, **77**, 3964.

which indicates that dissolution of gallium in the dichloride lowers the conductivity by about 3·7% in the temperature range studied. The results can be expressed by the equation $\log \kappa = 1{\cdot}235 - 815/T$, which corresponds to an activation energy E_κ of 3·73 kcal. mole^{-1}.

TABLE 1. *Electrical conductivity of fused gallium dichloride.*

Sequence	Temp.	κ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{2} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{2} cP ohm^{-1} mole^{-1})	Sequence	Temp.	κ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{2} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{2} cP ohm^{-1} mole^{-1})
21	167·4°	0·2510	29·13	103·9	6	177·0°	0·2743	32·06	102·0
20	168·4	0·2540	29·50	104·1	15	177·2	0·2753	32·12	102·0
19	169·8	0·2576	29·87	103·4	7	178·4	0·2780	32·47	101·6
18	171·2	0·2610	30·36	103·4	14	179·0	0·2789	32·58	101·2
1	172·4	0·2642	30·76	103·3	8	180·0	0·2817	32·92	101·3
2	173·5	0·2667	31·05	102·7	13	181·0	0·2844	33·26	101·2
17	173·8	0·2667	31·06	102·5	9	182·0	0·2873	33·62	101·0
3	174·2	0·2684	31·26	102·8	10	183·3	0·2903	33·99	100·8
4	175·0	0·2700	31·47	102·4	11	184·5	0·2932	34·35	100·5
16	175·5	0·2709	31·59	102·1	12	185·7	0·2963	34·74	100·1
5	176·0	0·2727	31·80	102·3					

TABLE 2. *Specific conductivity of a solution of gallium in gallium dichloride.*

Temp.	165·7°	166·7°	168·7°	170·7°	172·9°	175·0°	176·5°	178·0°	179·4°
κ (ohm^{-1} cm.$^{-1}$)	0·2383	0·2410	0·2454	0·2499	0·2557	0·2607	0·2645	0·2696	0·2723
Temp.	180·4°	181·5°	182·7°	183·5°	184·9°	186·4°	187·4°	189·0°	
κ (ohm^{-1} cm.$^{-1}$)	0·2746	0·2776	0·2802	0·2821	0·2857	0·2893	0·2916	0·2955	

TABLE 3. *Viscosity of gallium dichloride.*

Temp.	171·0°	173·6°	175·4°	177·0°	178·6°	179·7°	182·2°	184·3°	186·8°	188·8°
ν (cs)	1·412	1·367	1·346	1·315	1·289	1·280	1·258	1·222	1·183	1·165
η (cP)	3·416	3·302	3·247	3·172	3·106	3·081	3·025	2·935	2·835	2·788

TABLE 4. *Density, surface tension, and parachor of gallium dichloride.*

Temp.	d_4^t (g. ml.$^{-1}$)	γ (dyne cm.$^{-1}$)	$[P] = V_M \gamma^{\frac{1}{4}}$	Temp.	d_4^t (g. ml.$^{-1}$)	γ (dyne cm.$^{-1}$)	$[P] = V_M \gamma^{\frac{1}{4}}$	Temp.	d_4^t (g. ml.$^{-1}$)	γ (dyne cm.$^{-1}$)	$[P] = V_M \gamma^{\frac{1}{4}}$
166·7°	2·4249	57·68	319·8	171·1°	2·4190	56·41	318·6	175·0°	2·4134	(57·24)	(320·7)
168·0	2·4231	57·05	319·1	172·0	2·4178	55·80	318·0	176·0	2·4124	56·02	319·0
169·1	2·4216	56·08	317·7	173·2	2·4163	(54·55)	(316·4)	177·0	2·4116	55·36	318·2
170·1	2·4201	57·20	319·2	174·1	2·4150	55·25	317·5				

The dynamic viscosity of pure gallium dichloride is given by $\log \eta = -1{\cdot}768 + 1022/T$ from which the activation energy for viscous flow, E_η, is 4·68 kcal. mole^{-1}. Individual results for the range 171—189° are in Table 3 and the Figure. As the times of outflow were of the order of 70 sec., the figures are only precise to about 1 part in 500 but four significant figures have been retained to reduce errors in the computations of activation energy and reduced conductivity. At 172·4° the kinematic viscosity is $1{\cdot}38_8$ cs and the dynamic viscosity $3{\cdot}35_8$ cP.

The density of gallium dichloride in the temperature range 166—177° is shown in Table 4 and may be reproduced with a mean deviation of 2 in the last figure by the equation

$$d_4^t = 2{\cdot}4206 - 1{\cdot}36 \times 10^{-3}(t - 170)$$

At the m. p. the density of fused gallium dichloride is 2·4173, consistent with the only reference in the literature to the density,[14] *viz.*, that it is greater than that of Pyrex glass (2·238). Table 4 also records approximate values of the surface tension measured simultaneously with the density. Except for the two values in parentheses, we can express the results with a mean deviation of 0·4 dyne cm.$^{-1}$ by the equation

$$\gamma = 56{\cdot}6 - 0{\cdot}18(t - 170)$$

The molar surface free energy ($\omega = \gamma V_M^{\frac{1}{3}}$) is then

$$\omega = 1350 - 3{\cdot}9(t - 170)$$

Values of the parachor, $[P]$ are listed in the last column of Table 4. The function is constant, within experimental error, over the temperature range investigated and has a mean value of $318{\cdot}5 \pm 0{\cdot}5$. It is not possible to compare this with a theoretical value since there is no satisfactory method of calculating the parachor of fused salts.[17]

Gallium Dibromide, $Ga^+[GaBr_4]^-$.—The corresponding data on gallium dibromide are presented in Tables 5, 6, and 7 and are compared with those on the dichloride in the Figure. At the m. p. (166·7°) the specific conductivity is $0{\cdot}149_2$ ohm^{-1} cm.$^{-1}$ which is about half the value found for the dichloride. That this is predominantly a viscosity effect is shown by the fact that, although the molar conductivity, $19{\cdot}7_3$ cm.^{2} ohm^{-1} mole^{-1}, is still only about two-thirds that of the dichloride, the reduced conductivity, 136·3 cm.^{2} cP ohm^{-1} mole^{-1}, is rather greater than the corresponding figure for the dichloride (103·3 cm.^{2} cP ohm^{-1} mole^{-1}). The conductivity equation is $\log \kappa = 1{\cdot}142 - 865/T$, and the activation energies are $E_\kappa = 3{\cdot}96$ kcal. mole^{-1} and $E_\mu = 4{\cdot}16$ kcal. mole^{-1}.

TABLE 5. *Electrical conductivity of fused gallium dibromide.*

Sequence	Temp.	κ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{2} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{2} cP ohm^{-1} mole^{-1})	Sequence	Temp.	κ (ohm^{-1} cm.$^{-1}$)	μ (cm.^{2} ohm^{-1} mole^{-1})	$\mu\eta$ (cm.^{2} cP ohm^{-1} mole^{-1})
19	166·7°	0·1492	19·73	136·3	14	178·4°	0·1690	22·48	132·6
1	168·8	0·1521	20·13	135·5	15	180·1	0·1717	22·85	132·1
6	169·8	0·1543	20·44	135·3	16	181·1	0·1734	23·10	131·7
7	170·8	0·1560	20·67	135·0	17	182·2	0·1752	23·35	131·4
8	172·0	0·1581	20·95	134·7	18	183·3	0·1774	23·65	131·3
9	173·0	0·1601	21·23	135·1	5	184·8	0·1793	23·92	130·0
10	174·0	0·1616	21·45	134·3	4	186·2	0·1820	24·30	129·9
11	175·0	0·1631	21·67	133·9	3	187·8	0·1843	24·62	129·0
12	176·0	0·1650	21·94	133·8	2	189·0	0·1867	24·97	129·0
13	177·2	0·1670	22·20	133·1					

TABLE 6. *Viscosity of gallium dibromide.*

Temp.	165·9°	167·1°	170·0°	171·3°	172·7°	173·8°	176·5°	177·8°	179·9°	180·9°
ν (cS)	2·014	1·983	1·904	1·873	1·841	1·813	1·751	1·718	1·682	1·660
η (cP)	6·991	6·881	6·596	6·488	6·373	6·271	6·050	5·930	5·800	5·721

TABLE 7. *Density of molten gallium dibromide.*

Temp.	160·5°	162·5°	164·4°	166·4°	168·5°	170·5°	173·3°	175·1°
d_4^t (g. ml.$^{-1}$)	3·4820	3·4788	3·4751	3·4711	3·4682	3·4656	3·4604	3·4577
Temp.	176·6°	178·1°	179·7°	184·2°	186·8°	187·7°	189·6°	
d_4^t (g. ml.$^{-1}$)	3·4557	3·4521	3·4510	3·4408	3·4370	3·4357	3·4326	

The dynamic viscosities listed in Table 6 can be represented by $\log \eta = -1{\cdot}793 + 1158/T$. The activation energy for viscous flow, E_η, is 5·30 kcal. mole^{-1} and the viscosity at the m. p. is $6{\cdot}91_8$ cP. Outflow times were in the range 470—570 sec. and a complete temperature run lasted about 8 hr.

The densities in Table 7 lead to an equation

$$d_4^t = 3{\cdot}4656 - 1{\cdot}69 \times 10^{-3}(t - 170)$$

which reproduces the values with a mean deviation of 5 in the last decimal place. Surface tension was not measured because of a tendency to form small bubbles in the narrow capillary; this made differences in levels difficult to interpret but had little effect on the density results since it was possible to estimate the volume of the bubbles with a cathetometer.

DISCUSSION

When we started, the only information on the physical properties of gallium dichloride were its m. p. [4,13] and vapour pressure [14] together with statements that the solid

[17] McGowan, *Rec. Trav. chim.*, 1956, **75**, 193.

was diamagnetic [4] and that the fused compound conducted electricity.[18] Nothing was known of the properties of the dibromide. Recent investigations by means of Raman spectra [1,3] and *X*-ray analysis [2] have shown that both compounds are ionic and have the structures $Ga^+[GaCl_4]^-$ and $Ga^+[GaBr_4]^-$. The present results, summarized in Table 8, considerably extend our knowledge of the physical properties of these compounds and are entirely consistent with the ionic formulation.

The magnitude of the electrical conductivity of fused gallium dichloride and dibromide indicates that these compounds are true molten salts. At the m. p. (172·4°) the reduced conductivity of gallium dichloride is 103·3 and that of the dibromide at its m. p. (166·7°) 136·3 cm.^{2} cP ohm^{-1} mole^{-1}. These values may be compared with the reduced conductivity of a typical molten salt such as silver nitrate at its m. p. (208·9°).[19] The following data, extrapolated from figures in Landolt and Börnstein's tables, lead to a value for $\mu\eta$ of 136 which is virtually identical with the reduced conductivity of gallium dibromide: $AgNO_3$, $\kappa = 0{\cdot}641$ ohm^{-1} cm.$^{-1}$, $\eta = 4{\cdot}96$ cP, $d = 3{\cdot}974$ g. ml.$^{-1}$. More recent determinations on silver nitrate [20] vary among themselves by a few per cent. but are in essential agreement with these values.

The rather large activation energies of viscous flow (E_η in Table 8) are also typical of molten salts and are greater than values normally obtained for covalent liquids.[21] Moreover, the activation energy of viscous flow for both dihalides is appreciably greater than the activation energy of ionic migration, the values of the ratio E_η/E_μ being 1·23 for the dichloride and 1·27 for the dibromide (1·26 for silver nitrate). This suggests that the small Ga^+ ion is moving comparatively independently of the larger GaX_4^- ions, an effect which

TABLE 8. *Properties of the dihalides of gallium at their m. p.s.*

Property	$Ga^+GaCl_4^-$	$Ga^+GaBr_4^-$
Mol. wt.	281·27	459·10
M. p.	172·4°	166·7°
d (g. ml.$^{-1}$)	2·4173	$3{\cdot}471_2$
Temp. coeff. of d	$1{\cdot}36 \times 10^{-3}$	$1{\cdot}69 \times 10^{-3}$
V_M (ml. mole^{-1})	116·36	132·26
p (mm. Hg)	0·15 or 0·30 [a]	—
ΔH_{vap} (kcal. mole^{-1})	16·3 or 19·5 [a]	—
$\Delta H_{vap}/E_\eta$	3·49 or 4·17	—
γ (dyne cm.$^{-1}$)	56·2	—
Temp. coeff. of γ	0·180	—
ω (erg mole$^{-\frac{2}{3}}$)	1340	—
k (Eötvös)	3·9	—
$[P]$	318·5	—
v (cs)	$1{\cdot}38_8$	$1{\cdot}99_8$
η (cP)	$3{\cdot}35_5$	$6{\cdot}91_8$
ϕ (cP^{-1})	0·298	0·145
B (ml. cP g.$^{-1}$)	$6{\cdot}39 \times 10^{-2}$ [b]	$6{\cdot}69 \times 10^{-2}$ [b]
E_η (kcal. mole^{-1})	4·68	5·30
κ (ohm^{-1} cm.$^{-1}$)	$0{\cdot}264_2$	$0{\cdot}149_3$
μ (cm.^{2} ohm^{-1} mole^{-1})	$30{\cdot}7_6$	$19{\cdot}7_3$
$\mu\eta$ (cm.^{2} cP ohm^{-1} mole^{-1})	103·3	136·3
E_κ (kcal. mole^{-1})	3·59	3·96
E_μ (kcal. mole^{-1})	3·81	4·16
E_η/E_μ	1·23	1·27

[a] Calculated from data in ref. 14. [b] Batschinski's constant in the equation $v = b + B\phi$; see also ref. 8.

is frequently encountered in molten salts when the sizes of the cation and anion are very different.[22] This interpretation is consistent with two further observations which might

[18] Hampe, *Jahresber.*, 1888 (Part I), p. 388.
[19] Doucet, Le Duc, and Pannetier, *Compt. rend.*, 1953, **236**, 1018.
[20] Bokhovkin, *J. Gen. Chem. U.S.S.R.*, 1950, **20**, 397; Byrne, Fleming, and Wetmore, *Canad. J. Chem.*, 1952, **30**, 922; Pugsley and Wetmore, *ibid.*, 1954, **32**, 839; Kaoru Sakai, *J. Chem. Soc. Japan, Pure Chem. Sect.*, 1954, **75**, 182.
[21] Ward, *Trans. Faraday Soc.*, 1937, **33**, 88.
[22] Greenwood and Martin, *J.*, 1953, 1427.

otherwise be difficult to understand: (1) dissolution of gallium in the dichloride *lowers* the conductivity and *increases* the activation energy of conduction; (2) the molar volumes of the trihalides and dihalides are in the ratio 3 : 2, *i.e.*, in the ratio of the number of halogen atoms in the compounds.

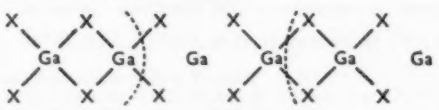
(1) The effect of dissolved gallium in lowering the conductivity of gallium dichloride provides an unusual example of the influence of disparity in size on the mobility of ions in molten salts. In the pure dichloride, most of the current will be carried by the small Ga^+ cation moving rapidly through the interstices of the relatively immobile network of $GaCl_4^-$ anions. When gallium is dissolved in this melt, chemical reduction occurs according to the equation

$$(n + 1)Ga^+GaCl_4^- + 2Ga = nGa^+GaCl_4^- + 4Ga^+Cl^-$$

The two added atoms of gallium increase the number of ions present from $(2n + 2)$ to $(2n + 8)$ so that, in effect, each added gallium atom is equivalent to three added ions. That this decreases rather than increases the conductivity is due to the fact that, in the solution, the gallium ions have to compete with the similarly sized chloride ions travelling in the opposite direction, with consequent decrease in mobility and increase in activation energy. The partial collapse of the anion network due to the replacement of the large $GaCl_4^-$ ions by the smaller Cl^- ions also contributes. A similar effect is observed in the classic case of α-silver iodide. Above the $\beta \rightarrow \alpha$ transition point (146°) the solid has an extraordinarily high unipolar electrical conductivity [23] because the relatively small silver ions can travel virtually unimpeded through the anion lattice of the crystal, there being thirty interstitial sites available for each two silver ions. However, when the crystal melts (554°) the iodide lattice collapses, reducing the number of interstices available to the silver ions and thus reducing their mobility. The mobility of the silver ions is further diminished by having to compete with the now mobile anions, so that the conductivity of the compound actually decreases on melting (from 2·64 to 2·36 ohm^{-1} $cm.^{-1}$) [23] though virtually all of the current is still carried by the cation ($E_\eta/E_\mu = 6{\cdot}4$).

An interesting rider to this description of the conduction process in the fused dihalides is that the reduced conductivity of the dibromide should be greater than that of the dichloride (as observed). It might at first be thought that the reverse would be true since the $GaBr_4^-$ ion is larger than the $GaCl_4^-$ ion and should move more slowly, thus lowering the conductivity, the cation being the same in each compound. However, if the conduction is unipolar, as postulated, the anions will be relatively immobile and the Ga^+ cation will move more freely through the interstices the greater the disparity in size between the cation and anion. This appears to be generally true of most molten salts; for example the reduced conductivity of the silver halides increases in the order $AgCl < AgBr < AgI$ and for the alkali metal chlorides the sequence is $KCl < NaCl < LiCl$.[22,24] In short, for a given series of compounds, $\mu\eta$ increases as the ratio E_η/E_μ increases.

(2) A second illustration of the ease with which Ga^+ ions can pack into the irregular interstices between the GaX_4^- ions comes from a comparison of the molar volumes of the fused dihalides and trihalides. The molar volumes of the dihalides are exactly two-thirds of the molar volumes of the corresponding trihalides. This implies that the gallium metal which is added to reduce the trihalides fits into existing " holes " in the liquid structure and causes no expansion of the melt, the factor of two-thirds arising because two moles of the trihalide furnish three moles of the dihalide:



[23] Tubandt and Lorenz, *Z. phys. Chem.*, 1914, **87**, 513.
[24] Karpachev, *J. Phys. Chem. U.S.S.R.*, 1935, **6**, 1079.

Values at the respective m. p.s being quoted, $2V_M(Ga_2Cl_6) = 343$ [25] and $3V_M(Ga_2Cl_4) = 349$; $2V_M(Ga_2Br_6) = 398$ [8] and $3V_M(Ga_2Br_4) = 397$. It is sometimes argued that a better comparison temperature is 10% above the absolute m. p. because of residual "solid" structure in the liquid near the m. p.[26] To check that the above agreement was not fortuitous, especially in view of the drastic structural changes which occur in the trihalides during melting,[27] molar volumes were also calculated by extrapolation to temperatures 10% above the absolute m. p. For the two chlorides the values of $2V_M$ and $3V_M$ are 356 and 357 respectively and for the bromides 410 and 406 ml. mole^{-1}. It is clear that the effect persists, the 23·0 ml. of gallium metal required for reduction of two moles of trihalide being completely accommodated in the interstices between the large anions.

TABLE 9. *Reduced conductivity of addition compounds of gallium trihalides at their respective m. p.s.*

Compound	Structure	$\mu\eta$	Ref.	Compound	Structure	$\mu\eta$	Ref.
$GaCl_3$,GaCl	$Ga^+GaCl_4^-$	103·3	—	$GaBr_3$,GaBr	$Ga^+GaBr_4^-$	136·3	—
$GaCl_3$,$POCl_3$	$POCl_2^+GaCl_4^-$	0·44	7	$GaBr_3$,$POBr_3$	$POBr_2^+GaBr_4^-$	1·0	8
$GaCl_3$,py	$[py_2GaCl_2]^+GaCl_4^-$	2·15	9	$GaBr_3$,py	$[py_2GaBr_2]^+GaBr_4^-$	3·1	10
$GaCl_3$,pip	$[pip_2GaCl_2]^+GaCl_4^-$	3·26	11	$GaBr_3$,pip	$[pip_2GaBr_2]^+GaBr_4^-$	3·9	10

A comparison of the reduced conductivities of the gallium dihalides with those of complexes of the gallium trihalides suggests that the complexes are incompletely dissociated into ions. Some figures are given in Table 9. The mean value of $\mu\eta$ for the complexes of gallium trichloride with phosphorus oxychloride, pyridine, and piperidine is less than $\mu\eta$ for gallium dichloride by a factor of 53. The factor for the bromides is 51. These differences are due both to mobility effects and to differences in the number of ions present.[23] It is unlikely that the high mobility of the small Ga^+ ion could account for a factor of more than about 5 and it is further apparent that the mobility is not the only factor operating since the reduced conductivities of the phosphorus oxyhalide complexes are not larger than those of the pyridine and piperidine complexes but are only about a quarter of these, despite the fact that their cations are smaller and therefore presumably more mobile. The remaining factor of 10—20 must presumably be ascribed to ion-pair formation though it is not yet possible to calculate the equilibrium constant from first principles in such complicated molten-salt systems. Indeed it is still difficult to explain even qualitatively why so many ionic complexes appear to be dissociated into kinetically free ions only to the extent of about 1—10%.

We thank the Chemical Society for a grant from the Research Fund and acknowledge the award of a University of Nottingham Research Scholarship (to I. J. W.).

THE UNIVERSITY, NOTTINGHAM. [*Received, December 19th*, 1957.]

[25] Greenwood and Wade, *J. Inorg. Nuclear Chem.*, 1957, **3**, 349.
[26] Bloom and Heymann, *Proc. Roy. Soc.*, 1947, *A*, **188**, 392.
[27] Greenwood and Worrall, *J. Inorg. Nuclear Chem.*, 1957, **3**, 357.

333. *The Reaction between Ammonia and Transition-metal Halides. Part IV.*[1] *The Reaction of Ammonia with Vanadium*(IV) *Chloride.*

By G. W. A. Fowles and D. Nicholls.

The reaction between liquid ammonia and vanadium(IV) chloride has been shown to give ammonium chloride and the ammonobasic vanadium(IV) chloride, $VCl(NH_2)_3$. The solubility of the latter in liquid ammonia containing dissolved ammonium salts (NH_4X) is attributed to the formation of a soluble ionic species $[NH_4][VClX(NH_2)_3]$. Tensimetric studies of the VCl_4–NH_3 system at $-36°$ and $-45°$ support these postulates.

The more covalent halides of the transition elements react with liquid ammonia to form ammonobasic halides and the ammonium halide; whenever the ammonobasic halide is insoluble in liquid ammonia it may be obtained pure by washing out the soluble ammonium halide. Recently, it has been shown that whereas titanium(IV) chloride [2] forms $TiCl(NH_2)_3$, and zirconium(IV) chloride [1] gives $ZrCl_3(NH_2)$, thorium(IV) chloride [1] forms only simple ammoniates with liquid ammonia. However, little reliable quantitative information is available concerning the corresponding reaction of vanadium(IV) chloride with liquid ammonia, since earlier workers did not appreciate the importance of studying it under rigorously anhydrous conditions. This can readily be seen from the analyses of the products obtained by Mertes and Fleck [3] and VanValkenburgh and Schoffmann,[4] where the total analysis (for vanadium, chlorine, and ammonia) is always considerably less than 100%; Mertes and Fleck in fact accounted for their discrepancy by assigning to their product an overall formula incorporating several molecules of water. Ephraim and Ammann [5] merely noted that a chocolate-brown solid was formed in the reaction but they quoted no analysis.

None of these workers seriously attempted to account for their results, and the idea that the chloride might be ammonolysed seems to have been neglected. In view of this, we have studied the vanadium(IV) chloride–liquid ammonia reaction both by removing soluble compounds by filtration and washing, and by tensimetric studies at $-36°$ and $-45°$.

Experimental

Materials.—Vanadium(IV) chloride was prepared from the elements [6] and distilled into ampoules.[7] Liquid ammonia (from Imperial Chemical Industries Limited) was dried with sodium before distillation *in vacuo* into the apparatus. Other reagents were of "AnalaR" grade; they were kept under a vacuum for several hours immediately before use in order to remove traces of moisture.

Analyses.—Nitrogen and chlorine were determined as described previously.[2] Vanadium was determined by oxidation to the quinquevalent state with potassium permanganate, followed by reduction to vanadium(IV) with mercury [8] and titration with standard permanganate.

Magnetic-moment Measurements.—These were made on a Gouy-type balance at room temperature (cf. Table 1); the magnet gave a maximum field strength of 8000 gauss with a pole-piece gap of 3 cm.

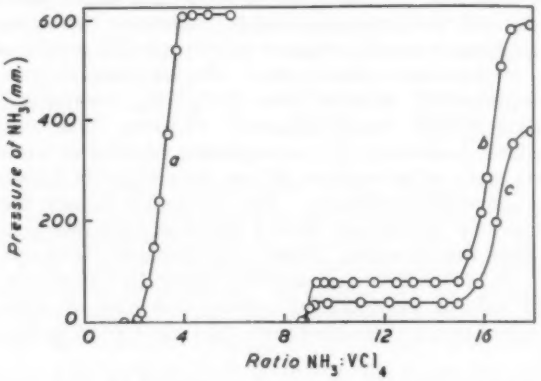
Reactions and Tensimetric Studies.—Reactions were studied in the usual type of all-glass closed vacuum system.[1,2] Stopcocks were greased with Silicone lubricant wherever they were likely to be exposed at all to vanadium(IV) chloride.

(i) An ampoule of vanadium(IV) chloride was broken *in vacuo*, and the contents were condensed into the reaction vessel; ammonia was condensed on the chloride and allowed to

[1] The paper by Fowles and Pollard, *J.*, 1953, 4128, is regarded as Part III.
[2] *Idem*, *J.*, 1953, 2588.
[3] Mertes and Fleck, *Ind. Eng. Chem.*, 1915, **7**, 1037.
[4] van Valkenburgh and Schoffmann, *Univ. Colorado Studies, Ser. D*1, No. 1, 1940, p. 23.
[5] Ephraim and Ammann, *Helv. Chim. Acta*, 1933, **16**, 1273.
[6] Fowles and Pleass, *J.*, 1957, 1674.
[7] *Idem*, *J. Chem. Educ.*, 1956, **33**, 640.
[8] McCay and Anderson, *J. Amer. Chem. Soc.*, 1922, **44**, 1018.

liquefy. The subsequent reaction gave a brown solution and a greenish-brown solid. The solution was filtered off through a filter-pad (no. 3 sinter), and the ammonia then condensed back on the solid product, which was shaken; the solution was then filtered again. The second filtrate was paler than the original solution, and subsequent filtrates were paler still, until after 4—5 washings they were colourless. The product was normally " pumped " between washings to break up the lumps and make subsequent extractions more efficient.

The insoluble greenish-brown product was ground to a fine powder by agitation with a glass-encased ball-bearing, and then quickly tipped, in a nitrogen atmosphere, through an adaptor into a magnetic-susceptibility tube. After its magnetic susceptibility had been measured, the substance was analysed (see Table 1). As the number of washings increased, the V : Cl : N ratio became close to the 1 : 1 : 3 expected for a composition $VCl(NH_2)_3$. Prolonged pumping around 40—60° gradually removed ammonia.



The magnetic moment is higher than might be expected for quadrivalent vanadium (1·73 B.M.), suggesting that a small amount of reduction has taken place. Because the ammonobasic vanadium(IV) chloride is insoluble in all solvents with which it does not react (*e.g.*, hexane, carbon tetrachloride, chlorobenzene) its spectra and molecular weight could not be studied.

TABLE 1. *Insoluble product of the reaction between liquid ammonia and vanadium*(IV) *chloride, washed with liquid ammonia.*

Run no.	Analyses (%) V	Cl	N	Mol. ratio V : Cl : N	No of washings	μ (B.M.)	Comments
1	30·7	32·9	30·8	1 : 1·54 : 3·65	6	—	Pumped at 40° for 6 hr. after washing.
2	33·3	32·3	30·1	1 : 1·39 : 3·39	8	—	Pumped at 50—60° between and after washings (15 hr. in all).
3	32·6	32·2	30·2	1 : 1·42 : 3·37	12	1·91	Pumped at 50—60° between and after washings (17 hr. in all).
4	30·4	32·6	28·6	1 : 1·54 : 3·42	15	2·03	Pumped 40—60° between and after washings (13 hr. in all).
5	33·8	31·8	28·9	1 : 1·31 : 3·12	21	1·93	Pumped 40—60° between and after washings (22 hr. in all).

Ammonia was allowed to evaporate from the final filtrate, and the residue which remained (accumulated from all the washings) appeared to be a mixture of a white and a greenish-brown substance. Loosely held ammonia was removed by warming the mixture to 40° and " pumping " for several hours, and the whole of the remaining solid was hydrolysed *in situ* and analysed. The results (Table 2) show that the soluble vanadium compound is most probably $VCl(NH_2)_3$, since the N : Cl ratio then corresponds closely to that for ammonium chloride.

(ii) *Effect of added salts on the solubility of* $VCl(NH_2)_3$ *in liquid ammonia.* Samples of various soluble salts were added to the ammonobasic vanadium(IV) chloride, and liquid ammonia was condensed on the mixture. The solid dissolved completely in liquid ammonia to a deep-brown solution when ammonium chloride, ammonium bromide, ammonium nitrate, or potassium iodide was added, but dissolved only to a very small extent in the presence of sodium nitrate.

(iii) *Tensimetric study of the* $VCl(NH_2)_3$–NH_3 *system.* To confirm the absence of ammonium chloride from the ammonobasic vanadium(IV) chloride, the $VCl(NH_2)_3$–NH_3 system was examined tensimetrically at −36°; the result is shown in plot *a*. The two molecules of ammonia which attached themselves fairly strongly to the ammonobasic chloride were lost on prolonged " pumping " at room temperature. When $VCl(NH_2)_3$ was heated *in vacuo* to ~300° for several hours it decomposed to give a black residue; this residue, which was hydrolysed only slowly by sodium hydroxide solution, gave an analysis corresponding to a V : Cl : N ratio of 1·00 : 1·13 : 0·82.

TABLE 2. *Analysis of the soluble portion.*

Run	N : Cl ratio * on the assumption that soluble vanadium is present as: $V(NH_2)_4$	$VCl(NH_2)_3$	$VCl_2(NH_2)_2$
1	1·00 : 1·17	1·00 : 0·99	1·00 : 0·81
2	1·00 : 1·23	1·00 : 1·00	1·00 : 0·81
3	1·00 : 1·13	1·00 : 0·98	1·00 : 0·86

* We assume that the soluble portion is a mixture of ammonium chloride and an ammonobasic vanadium(IV) chloride, so that, from the determined vanadium content, the associated nitrogen and chlorine required for each of the more likely compounds may be calculated. The N : Cl ratio for the remaining nitrogen and chlorine should then be 1 : 1, corresponding to ammonium chloride.

(iv) *Tensimetric studies of the* VCl_4–NH_3 *system.* A known excess of ammonia was condensed on a known weight of vanadium(IV) chloride, the mixture surrounded by a constant temperature bath, and the final equilibrium pressure of ammonia measured. Small portions of ammonia were successively removed and measured, and the new pressures measured after equilibrium had again been reached—this often required several days. The results of the investigations at −36° and −45° are illustrated in plots *b* and *c* respectively.

(v) *Thermal decomposition* (0—400°) *of the product of the* VCl_4–NH_3 *reaction.* After all ammonia had been removed at the reaction temperature (in the tensimetric runs) the mixed product was heated *in vacuo*, in stages, to 400°. Ammonia was lost steadily up to 200°; then a white sublimate, tinged with pink, began to be formed. The residue at this point was khaki-coloured with a violet tinge. Analysis gave: V, 26·9; Cl, 56·9; N, 16·3%; corresponding to V : Cl : N = 1 : 3·03 : 2·20 (duplicate V, 24·7; Cl, 58·1; N, 14·5%; V : Cl : N = 1 : 3·38 : 2·13). When further heated, to 400°, the substance became blue-black; its analysis gave a V : Cl : N ratio of 2·00 : 1·01 : 1·02. It was pyrophoric, and soluble in nitric acid with the evolution of nitrous fumes, only partly soluble in boiling sodium hydroxide solution, and almost insoluble in dilute sulphuric acid.

DISCUSSION

Vanadium(IV) chloride is undoubtedly ammonolysed by liquid ammonia, since not only is the product heterogeneous, but repeated extraction with liquid ammonia leaves an insoluble greenish-brown solid with an analysis close to that expected for $VCl(NH_2)_3$. When the initial product is extracted with liquid ammonia, about half of the vanadium dissolves to a greenish-brown solution; although no more dissolves after the first two or three washings, addition of ammonium chloride makes the insoluble residue dissolve. It seems therefore that $VCl(NH_2)_3$, or any other ammonobasic vanadium chloride formed, reacts with ammonium chloride produced in the initial reaction to form a soluble substance, and that once the ammonium chloride has been washed away the vanadium compound is insoluble.

An obvious explanation is that a soluble ionic species is formed by complexing of the type: $VCl(NH_2)_3 + NH_4Cl \longrightarrow [NH_4][VCl_2(NH_2)_3]$. Such behaviour is confirmed by the demonstration that the insoluble residue can be dissolved equally well by a liquid-ammonia solution of potassium iodide, so that it is a complex-forming action rather than just the effect of an acidic solution (ammonium salts in liquid ammonia). Analysis of the soluble portion of the products (Table 2) shows that the only ammonobasic vanadium(IV) chloride present in the mixture with ammonium chloride is $VCl(NH_2)_3$. The formula $[NH_4][VCl_2(NH_2)_3]$ does not necessarily imply a 5-co-ordinate state for vanadium, and the dimer $[NH_4]_2[V_2Cl_4(NH_2)_6]$ would, for instance, be equally satisfactory.

The insoluble residue apparently contains a little reduced vanadium, since the average magnetic moment is between 1·9 and 2·0 B.M. This is not entirely unexpected in such a basic solvent as ammonia, and it probably accounts for the apparent difficulty of removing the last traces of amonium chloride from the insoluble residue, where the V : Cl ratio is still 1 : 1·3 even when the compound has been washed twenty times. Any product involving a lower valency for vanadium formed will probably have a V : Cl ratio greater than 1 : 1 since the V–Cl bond will not be ammonolysed so readily as in vanadium(IV) compounds. The presence of a little tervalent vanadium seems a better explanation for the high V : Cl ratio than the presence of some still undissolved ammonium chloride, since the tensimetric study of the $VCl(NH_2)_3$–NH_3 system shows that there is no free ammonium chloride in the insoluble residue. Indeed, the ammonium chloride would make some of the insoluble residue soluble. A fairly stable 2-ammoniate $VCl(NH_2)_3,2NH_3$ is however formed, in which the vanadium atom presumably acquires an octahedral configuration. The insolubility of the ammonobasic vanadium(IV) chloride in liquid ammonia and other solvents with which it does not react suggests that it is highly polymeric. This polymeric nature is not incompatible with the ready complex-formation by potassium iodide and ammonium salts, in view of the similar reactions shown by the polymeric halides of mercury(II) and palladium(II).*

The tensimetric study of the vanadium(IV) chloride–ammonia system at −36° and −45° shows that two free molecules of ammonium chloride are produced by the ammonolysis of each molecule of vanadium(IV) chloride. In the tensimetric approach, the ammonium chloride is detected because it forms a triammoniate with a characteristic dissociation pressure, so that if any ammonium chloride undergoes complex-formation with the ammonobasic vanadium(IV) chloride, it will no longer be detected. Thus the reaction gives an initial mixture of $VCl(NH_2)_3$ and ammonium chloride, which then undergoes complex-formation:

$$VCl_4 + 6NH_3 = VCl(NH_2)_3 + 3NH_4Cl = [NH_4][VCl_2(NH_2)_2] + 2NH_4Cl$$

Only the two non-complex-forming ammonium chloride molecules are then detected. While the tensimetric studies show that between eight and nine molecules of ammonia are associated with each molecule of vanadium(IV) chloride at −36°, the equation shown above accounts for only six of these; the remaining two or three are weakly associated with the vanadium species.

Since washing experiments show that $VCl(NH_2)_3$ is the only ammonobasic vanadium(IV) chloride formed in the reaction, the tensimetric results cannot be interpreted as the formation of a mixture of $VCl_2(NH_2)_2$ with $2NH_4Cl$ (which reacts further only when the ammonium chloride is removed on washing).

When the tensimetric mixture is thermally decomposed, it loses ammonia, and around 200° ammonium chloride sublimes. In view of the high V : Cl ratio (1 : 3) found for the involatile product, it seems that there must be some interaction between the ammonobasic vanadium(IV) chloride and ammonium chloride, similar to that proposed for the tin(IV) chloride–ammonia system.[9] The decomposition is unfortunately too complicated for detailed study.

We thank the Esso Petroleum Company for a maintenance grant to D. N. and the Chemical Society for a research grant for the purchase of vanadium.

THE UNIVERSITY, SOUTHAMPTON. [*Received, November 19th*, 1957.]

* We are grateful to a Referee for pointing this out.

[9] Bannister and Fowles, *J.*, 1958, 751.

334. *Deuterium Exchange in the Aldol Condensation of Acetaldehyde.*

By R. P. Bell and Moyra J. Smith.

The aldol condensation of acetaldehyde has been carried out in borate buffers in deuterium oxide solution, and the amount of deuterium in the unchanged aldehyde has been studied as a function of aldehyde concentration and extent of reaction. The results are interpreted in terms of successive ionisation and condensation reactions, and values are obtained for the ratio of velocity constants and for the magnitude of the kinetic isotope effect.

It is generally agreed [1] that the aldol condensation of an aldehyde or ketone R·COMe, catalysed by hydroxyl ions, takes place according to the following scheme:

$$(a)\quad R\cdot COMe + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R\cdot CO\cdot CH_2^- + H_2O$$

$$(b)\quad R\cdot CO\cdot CH_2^- + R\cdot COMe \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} R\cdot CO\cdot CH_2\cdot CRMe\cdot O^-$$

$$(c)\quad R\cdot CO\cdot CH_2\cdot CRMe\cdot O^- + H_2O \underset{\text{Fast}}{\rightleftharpoons} R\cdot CO\cdot CH_2\cdot CRMe\cdot OH + OH^-$$

where k_1 and k_2 are second-order velocity constants, and k_{-1} and k_{-2} are first-order velocity constants. The condensation of acetone (R = Me) is reversible, and there is good evidence that the slow step in both directions is reaction (*b*), reaction (*a*) being effectively at equilibrium. The evidence for this is two-fold: first, the condensation reaction is kinetically of the second order with respect to acetone, and secondly it was shown by Bonhoeffer and Walters [2] that the rate of deuterium exchange of acetone in alkaline deuterium oxide is very much greater than its rate of condensation to give diacetone alcohol, being in fact equal to its rate of ionisation as measured by its reaction with iodine. These facts are consistent with $k_2[R\cdot COMe] \ll k_{-1}$ in the above scheme, and lead to the prediction that the reaction should not exhibit general base-catalysis, but only specific catalysis by hydroxyl ions, since the slow step (*b*) does not involve a proton-transfer.[3] This is consistent with the experimental facts, since the catalytic effect of ammonia and of primary and secondary amines (Miller and Kilpatrick [4]) is not a basic catalysis: tertiary amines and phenoxide ions do not catalyse this reaction [5] and the effect of the other amines has been traced to the formation of addition products.[6]

The aldol condensation of acetaldehyde (R = H) is irreversible, and shows different kinetic behaviour. The later stages of the reaction are complicated by crotonisation and further polymerisation, but it was found by Bell [7] that the reaction is essentially of the first-order with respect to acetaldehyde. Bell suggested originally that the slow step involved might be the reaction $Me\cdot CH(OH)_2 \longrightarrow Me\cdot CHO + H_2O$, catalysed by hydroxyl ions, but later work [8] showed that this reaction is much too fast to be rate-determining: moreover, aqueous solutions of acetaldehyde contain about 40% of unhydrated aldehyde,[9] which on this hypothesis should react very rapidly. It seems certain that the slow step is in fact reaction (*a*) above, corresponding to $k_2[Me\cdot CHO] \gg k_{-1}$. This implies that if the reaction takes place in deuterium oxide, no deuterium should become attached to carbon,

[1] See, *e.g.*, Frost and Pearson, "Kinetics and Mechanism," Wiley & Sons, New York, 1953, p. 291.
[2] Bonhoeffer and Walters, *Z. phys. Chem.*, 1938, **181**, *A*, 441.
[3] Bell, "Acid–Base Catalysis," Oxford Univ. Press, 1941, p. 124.
[4] Miller and Kilpatrick, *J. Amer. Chem. Soc.*, 1931, **53**, 3217.
[5] French, *ibid.*, 1929, **51**, 3215.
[6] Westheimer and Cohen, *ibid.*, 1938, **60**, 90; Westheimer and Jones, *ibid.*, 1941, **63**, 3283; Westheimer, *Ann. New York Acad. Sci.*, 1940, **39**, 401.
[7] Bell, *J.*, 1937, 1637.
[8] Bell and Higginson, *Proc. Roy. Soc.*, 1949, *A*, **197**, 141; Bell and Darwent, *Trans. Faraday Soc.*, 1950, **46**, 1; Bell and Clunie, *Proc. Roy. Soc.*, 1952, *A*, **212**, 33; Bell, Rand, and Wynne-Jones, *Trans. Faraday Soc.*, 1956, **52**, 1093.
[9] Bell and Clunie, *ibid.*, 1952, **48**, 439.

agreeing with the observations by Bonhoeffer and Walters [2] on the aldolisation of 10M-acetaldehyde solution. General base-catalysis would also be predicted on this interpretation: this has not been detected, but few experiments have been carried out to test this point.

Recent work by Broche [10] and by Broche and Gibert [11] has shown that the assumption k_2[Me·CHO] $\gg k_{-1}$ is justified only for high aldehyde concentrations. They studied the initial reaction velocity over a wide range of aldehyde and hydroxyl-ion concentrations, and found that in the range [Me·CHO] = 0·1—0·5 the order with respect to acetaldehyde was intermediate between 2 and 1, as would be predicted if k_2[Me·CHO] is of the same order of magnitude as k_{-1}. On this basis the reaction should be accompanied by isotopic hydrogen exchange at fairly low aldehyde concentrations, though not at the very high concentration used by Bonhoeffer and Walters.[2] The object of the present work was therefore to investigate deuterium exchange over a range of aldehyde concentrations.

Experimental

Kinetic and isotopic-exchange measurements were carried out at 25°.

Materials.—Acetaldehyde was distilled (b. p. 20·7—21°) in a current of oxygen-free nitrogen and condensed in a trap surrounded with solid carbon dioxide. It was immediately transferred and sealed in a number of small weighed bulbs previously swept out with nitrogen. These samples contained <0·2% of acid by titration, and gave a mass-spectrometer trace identical with that reported for pure acetaldehyde. Water used was twice distilled and freed from carbon dioxide by boiling it or by bubbling nitrogen through it. Deuterium oxide was supplied by the Norsk Hydro-Elektrisk Kvaelstof A/S and contained 99·7% of D_2O. Many experiments were carried out with deuterium oxide recovered from previous experiments, purified, and distilled to a constant density corresponding to 93% of D_2O. Inorganic reagents were of " AnalaR " grade.

Isotopic-exchange Measurements.—In these measurements the acetaldehyde was allowed to react for a known time in deuterium oxide containing either sodium hydroxide or a buffer solution, and the reaction then stopped by adding a slight excess of hydrochloric acid. In principle the extent of isotopic exchange could be determined by isotopic analysis of the aldol formed, of the water, or of the unchanged acetaldehyde. For dilute solutions the last of these is the most suitable, since the acetaldehyde can be removed either by volatilisation in a current of nitrogen or by extraction with an organic solvent. In some preliminary experiments the reaction mixture was saturated with sodium chloride and extracted with bromobenzene. After drying of the extract the acetaldehyde was removed by a current of nitrogen and condensed by solid carbon dioxide for examination in the mass spectrometer. Although these experiments gave qualitative evidence of the presence of deuterated acetaldehyde, the mass spectrometer traces were difficult to interpret quantitatively, since the samples obtained invariably contained bromobenzene and impurities probably derived from the oxidation or polymerisation of the aldehyde.

In the method finally adopted, the acetaldehyde was removed in a current of nitrogen and absorbed in a solution of 2 : 4-dinitrophenylhydrazine. The hydrazone was filtered off and heated with pyruvic acid to regenerate the acetaldehyde, which was then oxidised; the resulting water was analysed for deuterium by density determinations. The detailed procedure was as follows.

Three small bubblers were connected in series by glass joints. The first contained the reaction solution after acidification (about 2 c.c.) and the second a two-fold excess of 0·015M-2 : 4-dinitrophenylhydrazine in 1·6N-hydrochloric acid. The exact concentration of this solution was determined by titration with 0·0125M-potassium iodate, according to the equation $5(NO_2)_2C_6H_3{\cdot}NH{\cdot}NH_2 + 4KIO_3 + 9HCl = 3(NO_2)_2C_6H_3N_2Cl + 2(NO_2)_2C_6H_3I + 4KCl + 2ICl + 2N_2 + 12H_2O$ (cf. Iddles,[12, 13] Barker and Cole [14]), the end-point being detected by the disappearance of the iodine colour in a carbon tetrachloride layer. The third bubbler was a guard-tube containing sodium hydrogen sulphite solution, and any acetaldehyde escaping

[10] Broche, " Colloque National de Cinetique," Strasbourg, 1953.
[11] Broche and Gibert, *Bull. Soc. chim. France*, 1955, 131.
[12] Iddles and Jackson, *Ind. Eng. Chem., Anal.*, 1934, **6**, 454.
[13] Iddles, Rosen, and Hart, *ibid.*, 1939, **11**, 102.
[14] Barker and Cole, *J. Appl. Chem.*, 1955, **5**, 477.

absorption in the second bubbler was titrated after the experiment by the procedure described by Friedemann, Cotonio, and Shaffer: [15] the amount of acetaldehyde thus estimated was always negligible.

Oxygen-free nitrogen was passed through the three bubblers at about 40 c.c. per minute for 1½ hr. Control experiments showed that this was sufficient to remove 98% of the acetaldehyde. The 2 : 4-dinitrophenylhydrazone was then filtered off through a sintered-glass crucible, washed with 2N-hydrochloric acid and water, and weighed after at least 12 hr. *in vacuo* over sulphuric acid. The weight of the hydrazone served as a measure of the extent of reaction in the original mixture, and a second estimate was made by titrating the 2 : 4-dinitrophenylhydrazine remaining in the filtrate with potassium iodate solution, as described above. The two estimates agreed within better than 2%, but control experiments showed that the amounts of acetaldehyde thus calculated corresponded to only 93 ± 2% of that present in the original solution, and this was allowed for in the calculations. The formation of the hydrazone does not involve the hydrogen atoms of the acetaldehyde, and it is therefore safe to assume that no isotope effect is involved in this reaction, and that the degree of deuteration is not affected by the incompleteness of the conversion.

In a few experiments the infrared absorption of the solid 2 : 4-dinitrophenylhydrazone was examined.* An ordinary specimen showed a peak at 1365 $cm.^{-1}$, corresponding to the symmetrical deformation vibration of the CH_3 group, also peaks at 1126 and 1144 $cm.^{-1}$. A specimen obtained from an aldol condensation carried to 75% completion in 97% deuterium oxide with 0·1M-acetaldehyde showed no peak at 1365 $cm.^{-1}$, but a new one at about 1138 $cm.^{-1}$: this can be ascribed to C–D deformations, and the spectrum indicates that a considerable amount of deuteration had taken place. A third specimen was obtained from a reaction carried to 75% completion with 2·5M-acetaldehyde, and showed weak bands at both 1365 and 1138 $cm.^{-1}$. These observations indicate (in agreement with later results) that some deuteration does take place, and that its extent is greater in more dilute solutions of aldehyde, but the method is not suitable for a quantitative study, especially as the important band at 1138 $cm.^{-1}$ is obscured by those at 1126 and 1144 $cm.^{-1}$.

The normal oxidation procedure was carried out in a train of three small glass bubblers, of which the first two were fitted with cold fingers. In a typical experiment the first contained about 20 mg. of the dried hydrazone, together with about 0·1 g. of pyruvic acid and 3 c.c. of water. (Since no isotopic exchange takes place in acid solution between water and acetaldehyde or its hydrazone, the presence of water is not objectionable at this stage.) The second bubbler contained an oxidation mixture [16] consisting of about 0·5 g. of potassium persulphate and 0·05 g. of silver nitrate in about 0·6 c.c. of water mixed with glass beads. The amount of water was accurately known, since it enters into the calculation of the extent of deuteration. The third bubbler contained sodium hydrogen sulphite solution to absorb unoxidised acetaldehyde, which was estimated by titration.[14] In carrying out an oxidation the first bubbler was heated gently in a Bunsen flame and oxygen-free nitrogen passed for an hour at 20 c.c. per minute. The second bubbler was then heated to 70—78° and kept at this temperature until the black oxidation mixture had become colourless, usually about 20 min. Control experiments showed that under these conditions 95 ± 1% of the acetaldehyde was removed from the sample of hydrazone and transferred to the second bubbler, and that all the acetaldehyde remaining in the second bubbler was oxidised to carbon dioxide and water. On the other hand a considerable amount of acetaldehyde (about 30%) passed unchanged through the oxidation mixture: however, this was absorbed and titrated in the third bubbler and could be allowed for in making the final calculation. In these reactions the isotopically substituted hydrogen atoms of the acetaldehyde are not involved until the last stage in which acetic acid is oxidised to carbon dioxide and water. Control experiments showed that no acetic acid escaped oxidation, and there is therefore no danger of an appreciable isotopic discrimination in the conversion of the acetaldehyde into water.

The water in the oxidation mixture was distilled off into a trap surrounded by solid carbon dioxide, and distilled a second time after being made alkaline with sodium hydroxide. A final

* These measurements were carried out by Mr. O. G. Malan of this laboratory, to whom our thanks are offered.

[15] Friedemann, Cotonio, and Shaffer, *J. Biol. Chem.*, 1927, **73**, 342.

[16] Calvin, Heidelberger, Reid, Tolbert, and Yankwich, "Isotopic Carbon," Wiley & Sons, New York, 1949, p. 94.

XUM

distillation was carried out at 1 mm., and it was found that further distillations produced no change in the density. Densities were determined by measuring the rate of fall of a drop of water in a column of *o*-fluorotoluene at 26·8°.[17] A drop of constant size (about 8 mm.³) was formed below the surface of the *o*-fluorotoluene at the tip of a graduated capillary, and was detached by raising the capillary slowly out of the liquid. The *o*-fluorotoluene was contained in a vertical tube 50 cm. high and 1 cm. in diameter, and the falling drop was timed between two marks on the lower part of the tube 15 cm. apart. The time of fall for pure water was about 165 sec., the reproducibility being about ±0·5 sec. The apparatus was calibrated with sucrose solutions of known density, and also with deuterium oxide solutions of known composition. The density changes measured were usually in the range 30—100 p.p.m., and in this range 1 p.p.m. produces a change of about 0·5 sec. in the time of fall. The same change would be produced by a temperature variation of 0·001°: the thermostat fluctuations did not exceed this over a period of a few hours, but there were larger variations over long periods. For this reason each estimation was coupled with a calibration in which two standard solutions were used closely bracketing the unknown density, which was then determined by linear interpolation.

Density changes were referred to boiled-out distilled water which had been subjected to the same distillation as the test samples. Control experiments showed that water of the same density (within 1 p.p.m.) was obtained when the whole procedure of an exchange experiment was carried out with ordinary distilled water in place of deuterium oxide.

All the exchange experiments were carried out in a buffer solution made by adding solid borax and concentrated sodium hydroxide solution to deuterium oxide in amounts sufficient to give a solution with $[D_3BO_3] = 0{\cdot}02$, $[D_2BO_3^-] = 0{\cdot}18$. This solution gives convenient amounts of reaction for times of a few hours, and is insensitive to traces of carbon dioxide. The results obtained are tabulated. Since the extent of deuteration is small in all the experiments it has been expressed in terms of the monodeuterated species $CH_2D{\cdot}CHO$.

Deuterium exchange in borate buffer solution at 25°.

a = Initial acetaldehyde concentration in moles/l.
x = Fraction of acetaldehyde converted into aldol.
y = Fraction of initial acetaldehyde appearing as monodeuteroacetaldehyde.

$100a$	4·94	4·78	5·43	8·42	8·24	7·76	7·52	7·65	15·3	15·8	14·5	30·8	140
$100x$	15	23	30	10	19	27	29	43	25	37	38	35	64
$100y$	2·5	5·9	6·3	1·0	3·0	3·7	4·8	6·2	2·4	3·8	3·9	2·2	0·15

Discussion

It is apparent from the Table that for a given initial concentration of acetaldehyde the percentage deuteration increases as the reaction progresses (at least for the first half of the reaction), while for a given extent of reaction it decreases with increasing acetaldehyde concentration, becoming almost zero with an initial aldehyde concentration of 1·4M. These findings are in qualitative agreement with the reaction scheme given in the introduction, and will now be treated quantitatively.

The buffer solution used contains three acid–base systems, D_2O–OD^-, D_3O^+–D_2O and D_3BO_3–$D_2BO_3^-$, each of which can take part in the interconversion of the aldehyde molecule and its anion. However, since all the experiments were carried out in the same buffer solution, the forward and the reverse reactions can be characterised by first-order velocity constants k_1 and k_{-1}. The rate of production of the anion A^- from the aldehyde AH is thus $k_1[AH]$. As soon as some deuteration has taken place anions can also be produced from AD; since a proton is always lost considerably more rapidly than a deuteron, the appropriate velocity constant will be taken as $\frac{2}{3}k_1$, the factor $\frac{2}{3}$ being a statistical factor for comparing the groups CH_2D and CH_3. This gives $k_1([AH] + \frac{2}{3}[AD])$ for the rate of production of A^-, where A^- represents both $CH_2{\cdot}CHO^-$ and $CHD{\cdot}CHO^-$. A^- can now react in two ways, either with the acids in the solution, which increases the deuterium content of the acetaldehyde, or with a second molecule AH or AD to give aldol. The rates of these two processes are respectively $k_{-1}[A^-]$ and $k_2[A^-]([AH] + [AD])$, where

[17] Keston, Rittenberg, and Schoenheimer, *J. Biol. Chem.*, 1936, **122**, 227.

it is assumed that isotopic substitution does not affect the velocity constant k_2 for the condensation reaction. This gives the following expressions:

(1) Rate of deuteration $= \dfrac{k_1k_{-1}([AH] + \frac{2}{3}[AD])}{k_{-1} + k_2([AH] + [AD])}$

(2) Rate of aldolisation $= \dfrac{2k_1k_2([AH] + \frac{2}{3}[AD])([AH] + [AD])}{k_{-1} + k_2([AH] + [AD])}$

where the factor of 2 in the second equation arises because each condensation reaction removes two molecules of acetaldehyde. However, equation (1) cannot be applied directly to our results, since we have measured only the deuterium in the remaining acetaldehyde, and not in the aldol, and must therefore allow for the removal of deuterium by the reactions $CH_2D{\cdot}CHO + CH_2{\cdot}CHO^-$, $Me{\cdot}CHO + CHD{\cdot}CHO^-$, and $CH_2D{\cdot}CHO + CHD{\cdot}CHO^-$.

Arguments similar to the above give:

$$\text{(3) Rate of loss of deuterium} = \frac{\frac{2}{3}k_1k_2[AD]([AH] + 2[AD])}{k_{-1} + k_2([AH] + [AD])} + \frac{k_1k_2[AH][AD]}{k_{-1} + k_2([AH] + [AD])}$$
$$= \frac{\frac{5}{3}k_1k_2[AD]([AH] + \frac{7}{5}[AD])}{k_{-1} + k_2([AH] + [AD])} \simeq \frac{\frac{5}{3}k_1k_2([AH] + \frac{2}{5}[AD])}{k_{-1} + k_2([AH] + [AD])}$$

The last approximation simplifies the subsequent calculation, and is legitimate since [AD] never exceeds 6% of [AH]. From (1) and (3) we have the following expression for the net rate of formation of $CH_2D{\cdot}CHO$, introducing the symbols used in Table 1:

$$\text{(4)} \qquad \frac{dy}{dt} = \frac{k_1(1 - x - \frac{1}{3}y)(k_{-1} - \frac{5}{3}k_2ay)}{k_{-1} + k_2a(1 - x)}$$

Combining (2) and (4) gives

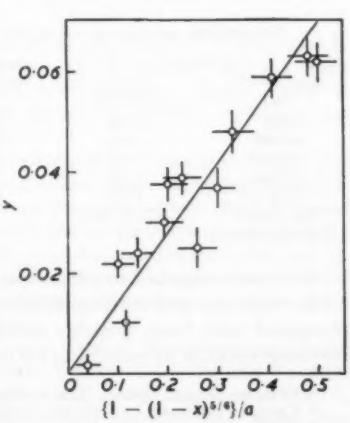
$$\text{(5)} \qquad dy/dx = (k_{-1} - \tfrac{5}{3}k_2ay)/2k_2a(1 - x)$$

and hence on integration

$$\text{(6)} \qquad y = \tfrac{3}{5}\{1 - (1 - x)^{5/6}\}k_{-1}/k_2a$$

which for small values of x reduces to $y = k_{-1}x/2k_2a$.

The Figure shows a plot of y against $\{1 - (1 - x)^{5/6}\}/a$. Within the rather large experimental error the points corresponding to aldehyde concentrations 0·05—1·4M and 10—64% reaction fall on a single straight line, thus confirming the reaction scheme proposed. The slope of the line gives $k_{-1}/k_2 = 0{\cdot}023$ mole $l.^{-1}$. The corresponding value in Broche's measurements[10] in light water at 25° is 0·100, and if k_2 is the same in both solvents this gives $k_{-1}(H_2O)/k_{-1}(D_2O) = 4{\cdot}3$. If in our experiments all the deuteration is brought about by D_2O molecules (*i.e.*, if the aldolisation is catalysed specifically by OD^-), then 4·3 represents the ratio of the rates of proton and deuteron transfer from H_2O and D_2O molecules respectively. Actually there is some evidence from unpublished measurements in this laboratory that the aldol condensation exhibits appreciable general basic catalysis by borate ions: if this is so, some of the deuteration is brought about by D_3BO_3 molecules, and 4·3 is then a lower limit for the ratio $k_{-1}(H_2O)k_{-1}(D_2O)$. There are no measurements of isotope effects for other reactions of H_2O and D_2O with anions, but the figure 4·3 is well below the maximum ratio 10·6 predicted for 25° from the zero-point energies of O–H and O–D bonds (cf.



Wiberg [18]). A full interpretation demands a further kinetic study in buffer solutions, and would also take into account the fact that the exchange experiments were carried out in 93% rather than 100% D_2O.

It is therefore concluded that the deuterium exchange observed during the aldol condensation of acetaldehyde is quantitatively consistent with a mechanism in which the consecutive steps become of comparable speed at low acetaldehyde concentrations, and with a kinetic isotope effect of reasonable magnitude.

We thank the Ontario Research Foundation for a grant to one of us (M. J. S.).

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, September 24th*, 1957.]

[18] Wiberg, *Chem. Rev.*, 1955, **55**, 713.

NOTES.

335. *Acid-catalysis of Glycol Fission by Lead Tetra-acetate.*

By R. P. BELL, V. G. RIVLIN, and WILLIAM A. WATERS.

COMPREHENSIVE studies by Criegee and his colleagues [1,2] of 1 : 2-glycol fission by lead tetra-acetate have shown that the reaction velocities depend very markedly on solvent and that *cis*- and *trans*-isomers are affected to different extents by solvent changes. Published data, though seldom extensive enough for critical review, show excellent concordance with true second-order kinetics [1-3] though this is not always the case for glycol fission by other reagents.[4]

We have measured the rates of oxidation, by lead tetra-acetate in glacial acetic acid at 25°, of pinacol and of *trans*- and *cis-cyclo*hexane-1 : 2-diol and have confirmed that each is of the second order. Moreover, all these oxidations are prone to acid-catalysis, as the tabulated results, obtained by the addition of trichloroacetic acid, show: the catalytic coefficients, $\Delta k_{bi}/[\text{Acid}]$, depend on the structure of the glycol and follow the order of the reaction velocity in the absence of added catalyst. Standard experimental procedures [3] were used for the kinetic work; the pure *cyclo*hexanediols were available from a previous investigation.[5]

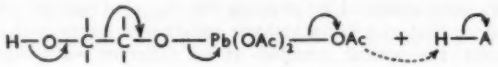
Oxidations of glycols in acetic acid at 25° in the presence of trichloroacetic acid.

Pinacol		*trans-cyclo*Hexane-1 : 2-diol		*cis-cyclo*Hexane-1 : 2-diol	
Acid added (M)	k_{bi} (min.$^{-1}$)	Acid added (M)	k_{bi} (min.$^{-1}$)	Acid added (M)	k_{bi} (min.$^{-1}$)
0·00	0·74	0·00	0·52	0·00	10·2
0·099	0·92	0·070	0·596	0·052	11·6
0·200	1·07	0·164	0·67	0·104	12·7
0·256	1·16	0·294	0·80	0·150	14·0
0·378	1·40	0·493	0·99	—	—
Δk/[Acid]	1·71 ± 0·1	—	0·95 ± 0·06	—	25·5 ± 1·6
$(\Delta k/k_0)$/[Acid]	2·3	—	1·83	—	2·5

Even more marked catalysis was observed by use of small concentrations of the stronger acids, sulphuric and methanesulphonic acid, but then the apparent second-order constants decreased with time, possibly owing to concurrent removal of pinacol by acid-catalysed rearrangement or by esterification of the glycols with acetic acid.

[1] Criegee, Höger, Huber, Kruck, Marktscheffel, and Schellenberger, *Annalen*, 1956, **599**, 81.
[2] Criegee, Buchner, and Walther, *Ber.*, 1940, **73**, 563, 571.
[3] Bell, Sturrock, and Whitehead, *J.*, 1940, 82; Cordner and Pausacker, *J.*, 1953, 102.
[4] Drummond and Waters, *J.*, 1953, 3119; Duke and Forist, *J. Amer. Chem. Soc.*, 1949, **71**, 2790; Duke and Bremer, *ibid.*, 1951, **73**, 5179.
[5] Levesley, Waters, and Wright, *J.*, 1956, 840.

This demonstration of acid-catalysis of glycol fission by lead tetra-acetate indicates that in acetic acid the process is heterolytic. If the oxidation involves a process of covalent O–Pb bond formation, *e.g.*, $R_3C{\cdot}OH + Pb(OAc)_4 \longrightarrow R_3C{\cdot}O{\cdot}Pb(OAc)_3 +$ HOAc, then this, being akin to the esterification of an alcohol, may well be influenced by acid-catalysis. Again the base-catalysed process of glycol fission, recently suggested by Criegee,[1] has an obvious counterpart in the following acid-catalysed process:



THE DYSON PERRINS AND PHYSICAL CHEMISTRY LABORATORIES,
OXFORD.
[*Received, November 11th*, 1957.]

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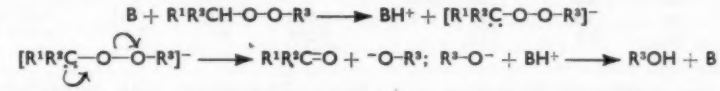
336. *The Kinetics of the Base-catalysed Decomposition of Benzyl* tert.*-Butyl Peroxide.*

By R. P. BELL and A. O. MCDOUGALL.

KORNBLUM and DELAMARE [1] showed that *tert.*-butyl 1-phenylethyl peroxide decomposes in presence of bases to acetophenone and *tert.*-butyl alcohol, and suggested the following mechanism for the base-catalysed decomposition of this type of peroxide:



The first two steps are considered to be synchronous and rate-determining, and the third rapid. Recently Kornblum and Clark [2] studied the kinetics of decomposition of benzyl *tert.*-butyl peroxide and *tert.*-butyl 1-phenylethyl peroxide in *tert.*-butyl alcohol, catalysed by piperidine, and showed that the reaction exhibits a large deuterium isotope effect; this would be expected from the above mechanism, which involves a proton-transfer in the rate-determining step. Kornblum and Clark followed the reaction by precipitating benzaldehyde 2 : 4-dinitrophenylhydrazone. We now describe an optical method, and deal mainly with catalysis by tertiary bases.

Experimental.—A sample of benzyl *tert.*-butyl peroxide was kindly provided by Professor N. Kornblum of Purdue University, U.S.A., whom we thank. Chlorobenzene and *tert.*-butyl alcohol were of " Laboratory Reagent " grade. Piperidine, triethylamine, collidine, and 2 : 6-lutidine were commercial products distilled from solid sodium hydroxide. Solvents and catalysts were examined spectrophotometrically before use.

The reaction was followed by measurements of optical density with a Unicam S.P. 500 spectrophotometer, the appearance of the carbonyl absorption band of benzaldehyde with a maximum at about 3280 Å being used. Measurements were made in the range 3000—3700 Å, where the absorption of the peroxide is negligible. The peroxide concentration was about 0·05M. At 25° and 40° the reaction took place in a thermostatically controlled cell holder in the spectrophotometer; at 60° and 80° the mixture was placed in a thermostat, and samples were removed and examined after cooling. In the absence of base the peroxide solutions showed no change of absorption under the conditions of the kinetic measurements.

A few experiments were made with piperidine in *tert.*-butyl alcohol (Kornblum and Clark's catalyst). The absorption changed with time, but the resulting spectrum did not resemble that of benzaldehyde: in particular there was little absorption in the neighbourhood of 3300 Å. This suggests that the benzaldehyde originally formed reacts rapidly with piperidine, and it was found that the carbonyl absorption of a solution of benzaldehyde disappears

[1] Kornblum and H. E. DeLaMare, *J. Amer. Chem. Soc.*, 1951, **73**, 880.
[2] Kornblum and Clark, personal communication from Professor Kornblum.

instantaneously on addition of piperidine. Possible reactions are $Ph{\cdot}CHO + C_5H_{10}NH \longrightarrow Ph{\cdot}CH(OH){\cdot}NC_5H_{10}$, or $Ph{\cdot}CHO + 2C_5H_{10}NH \longrightarrow Ph{\cdot}CH(NC_5H_{10})_2 + H_2O$. Such reactions presumably occurred in Kornblum and Clark's experiments, but the condensation products were apparently decomposed by the acid solution of 2 : 4-dinitrophenylhydrazine used as an analytical reagent.

When tertiary amines in chlorobenzene were used as catalysts, the spectrum of the peroxide was gradually replaced by that of benzaldehyde. Each reaction followed first-order kinetics, and velocity constants were obtained by plotting log $(r_\infty - r_t)$ against t, where r_t is the optical density at time t, and r_∞ that of a benzaldehyde solution of equivalent concentration. Plots for any one experiment, the optical densities at six different wavelengths being used, were parallel, showing that benzaldehyde is produced quantitatively.

The observed first-order velocity constants k_1 are given in the Table. The results for triethylamine and collidine at 80° show that k_1 is proportional to the catalyst concentration, and the last column gives the catalytic constant $k_2 = k_1/[\text{catalyst}]$.

Catalysis by tertiary amines in chlorobenzene.

[Catalyst]	Temp.	10^4k_1 (sec.$^{-1}$)	10^5k_2 (l. mole^{-1} sec.$^{-1}$)	
Triethylamine, $K_A = 1{\cdot}6 \times 10^{-11}$.				
0·512	25°	26	5·1	
0·494	40	90	22	
0·148	60	89	60	
0·011	80	12·9	117	
0·021	80	23	109	
0·050	80	65	130	Mean
0·079	80	96	121	118
0·195	80	219	112	
Collidine, $K_A = 3{\cdot}4 \times 10^{-8}$.				
0·109	80°	2·8	2·6	
0·213	80	5·1	2·4	Mean
0·322	80	6·2	1·9	2·3
0·439	80	9·9	2·2	
2 : 6-*Lutidine*, $K_A = 1{\cdot}9 \times 10^{-7}$.				
0·203	80	0·81	0·40	Mean
0·294	80	1·21	0·41	0·41

Discussion.—Although Kornblum and Clark's observations with piperidine might have been complicated by reaction between piperidine and benzaldehyde, this reaction is fast, so that the measured velocity was probably that of the decomposition of the peroxide, and their interpretation of the observed hydrogen isotope effect can be accepted.

Our other results show that solutions of tertiary amines in chlorobenzene catalyse the decomposition without complication, the velocity being proportional to the catalyst concentration. The values of the catalytic constant of triethylamine at four temperatures lead to an activation energy of about 12 kcal./mole and a collision factor of about 10^4 l. mole^{-1} sec.$^{-1}$. Similar values ($E = 14$ kcal./mole, $A = 10^5$ l. mole^{-1} sec.$^{-1}$) were found by Kornblum and Clark for catalysis by piperidine in *tert.*-butyl alcohol, again suggesting that they were measuring the rate of peroxide decomposition. Both collision factors are very much smaller than the values predicted by simple collision theory (10^{11}—10^{12} l. mole^{-1} sec.$^{-1}$) as is frequently found for reactions in which a highly polar transition state is formed from two uncharged reactants; this is consistent with the mechanism above.

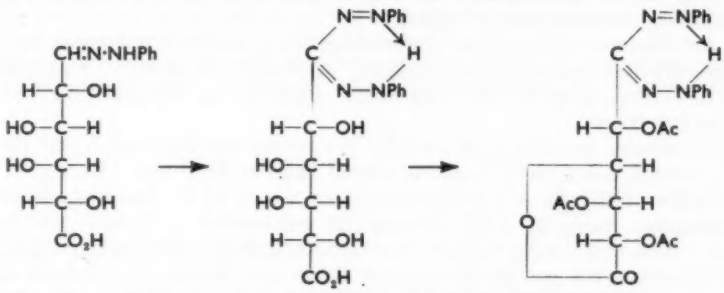
The catalytic constants of the three tertiary amines studied increase with increasing basic strength, K_A in the Table being the acid dissociation constant of the amine cation at 25°. The values suggest that in the Brönsted equation $k_2 = G\ (1/K_A)^\beta$, $\beta < 1$ as is commonly the case. The reaction thus exhibits general base catalysis, in harmony with the mechanism suggested by Kornblum and DeLaMare.[1]

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, December 23rd*, 1957.]

337. *Preparation of the Formazan from* D-*Galacturonic Acid.*

By L. Mester and E. Móczár.

Recently we reported the preparation of some novel types of sugar formazan.[1] It has now been found that D-galacturonic acid phenylhydrazone [2] with diazotized aniline in pyridine solution also gives a formazan; owing to the presence of the carboxyl group this dissolves more readily in water than the simple sugar formazans. Acetylation leads to the tri-*O*-acetate of the formazan of D-galacturonic acid lactone.



Experimental.—We are grateful to Miss Ilona Batta for the microanalyses.

D-*Galacturonic acid diphenylformazan.* The barium salt (1 g.) of D-galacturonic acid phenylhydrazone [2] was shaken for 30 min. with 50% ethanol (17 ml.) and 0·5N-sulphuric acid (5·34 ml.). Barium sulphate was filtered off and washed with 50% ethanol (15 ml.). After 6 hr. pyridine (5 ml.) was added and 5 min. later the product was coupled at −5° with a diazonium solution (2·6 ml.) prepared from aniline (0·26 g.). The mixture was set aside for 40 min., then ice–water (30 ml.) was added. Next day, the dark red precipitate (0·12 g.) was removed, the mother liquor evaporated *in vacuo* to one-third its volume, and the red needles which separated were removed (0·201 g.; m. p. 147—148°). Recrystallized from alcohol the *formazan* had m. p. 151—152° (0·327 g., 30%) (Found: C, 55·5; H, 5·2; N, 14·1. $C_{18}H_{20}O_6N_4$ requires C, 55·7; H, 5·2; N, 14·4%).

D-*Galacturonic lactone diphenylformazan tri*-O-*acetate.* D-Galacturonic acid diphenylformazan (0·2 g.) was set aside in pyridine (3 ml.) and acetic anhydride (3 ml.) overnight, then poured into water (20 ml.). The precipitated red *acetate* was recrystallized from alcohol and had m. p. 187° (0·16 g.) (Found: N, 11·1; OAc, 26·3. $C_{24}H_{24}O_9N_4$ requires N, 11·3; OAc, 26·0%).

Institute of Organic Chemistry,
Technical University of Budapest, Hungary. [*Received, March* 18*th*, 1957.]

[1] Mester and Móczár, *J.*, 1956, 3228.
[2] Niemann, Schoeffel, and Link, *J. Biol. Chem.*, 1933, **101**, 337.

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338. *Some Constituents of the Broad Bean.*

By M. T. J. Abbot, John Frederick Grove, and P. McCloskey.

During an investigation into the translocation of some derivatives of griseofulvin in the broad bean *Vicia faba* L.,[1] kaempferol (3 : 5 : 7 : 4′-tetrahydroxyflavone) was isolated from the shoots and fumaric acid and betulin from the roots of untreated plants. All these compounds have been obtained frequently from plant sources but have not hitherto been reported as constituents of the broad bean.

Kaempferol was isolated from the ether extract of shoot tissue which had been macerated in water; when the shoots were macerated in aqueous sodium hydrogen carbonate the

[1] Crowdy, Green, Grove, McCloskey, and Morrison, to be published.

extract contained *p*-hydroxybenzoic acid instead of kaempferol. It was subsequently established spectrophotometrically that the latter was decomposed to *p*-hydroxybenzoic acid in sodium hydrogen carbonate solution in the presence of air. In the initial (rapid) stage of the reaction the intensity of the kaempferol peak at 405 mμ decreased and there was a corresponding increase in the intensity of a new peak at 332 mμ due to the (intermediate) formation of a chromophore of *p*-hydroxyaroyl anion type. There was a sharp isosbestic point at 359 mμ. In the second (slow) stage of the reaction the intensity of the 332 mμ peak decreased and a new peak, due to the chromophore of *p*-hydroxybenzoic acid anion (present also in phloroglucinolcarboxylic acid) appeared at 280 mμ: *p*-hydroxybenzoic acid was recovered and identified.

Shaw and Simpson [2] showed that the introduction of a 5-hydroxyl group into flavone or 3-hydroxyflavone increased the carbonyl stretching frequency. Kaempferol and quercetin (C=O frequencies for both compounds: 1656 cm.$^{-1}$ in dioxan) provide additional examples of this effect.

Many flavanoids show biological activity (for review see Willaman [3]) and the parent substance, flavone, has activity [4] against several fungi at 50 μg./ml. Kaempferol might therefore be responsible for any natural resistance shown by *V. faba* towards attack by fungal pathogens: however, it failed to inhibit germination of *Botrytis allii* spores at 100 μg./ml. It had no activity against *Bacillus subtilis* at the same concentration.

A triterpene alcohol present in the root tissue was identified as betulin after the molecular weight of its diacetate had been determined by the *X*-ray method. *X*-Ray crystallographic data for betulin ethanolate and diacetate are presented below. Betulin had no activity at 100 μg./ml. against *B. allii* or against *B. subtilis*.

Experimental.—Microanalyses are by Messrs. W. Brown and A. G. Olney.

The raising and harvesting of the plants, *Vicia faba L.* var. Suttons Dwarf, have been described.[1] Shoots (840 g.) and roots (371 g.) were separately macerated in water and the acidified aqueous macerates extracted with ether. The recovered solutes were subjected to 50 transfers in a counter-current distribution apparatus, carbon tetrachloride–methanol–water (62 : 35 : 3) being used, and the solutions in the equilibrium tubes were examined spectrophotometrically for specific ultraviolet absorption.

Extract of shoots (3·8 g.). The contents of tubes 35—48 (particularly tube 43) showed maxima near 270 and 370 mμ. The solute from tubes 39—47 was separated into neutral, acidic, and phenolic fractions. The phenolic fraction, m. p. 230° (decomp.), was crystallised twice from ethanol–light petroleum (b. p. 60—80°) and formed lemon-yellow microcrystals of kaempferol (40 mg.), m. p. 282° (decomp.) [Found: C, 62·7; H, 3·8; OMe, nil %; *M* (Rast), 261. Calc. for $C_{15}H_{10}O_6$: C, 62·9; H, 3·5%; *M*, 286]; $\lambda_{max.}$ ~245, 267, ~295, ~325, 370 mμ, log ε 4·22, 4·32, 4·03, 4·12, 4·42 respectively (in ethanol); 3345 and 3145 cm.$^{-1}$ (OH) and 1659 cm.$^{-1}$ (C=O) ("Nujol" mull). Identity was established by comparison of m. p. and spectra with those of authentic material and by preparation of the tetra-acetate, needles (from methanol), m. p. and mixed m. p. 118—120° (loss of solvent), resetting and remelting at 182° (Found in material dried at 100° *in vacuo*: C, 60·7; H, 4·1. Calc. for $C_{23}H_{18}O_{10}$: C, 60·8; H, 4·0%). The kaempferol content of the shoot extract estimated spectrophotometrically corresponded to 180 μg./g. fresh weight of shoot tissue.

When the shoots were macerated in sodium hydrogen carbonate the ethereal extract contained only a trace of kaempferol (estimated spectrophotometrically) but the acidic fraction from tubes 35—48 showed a broad maximum near 280 mμ in 0·1N-sodium hydroxide. The acid fraction was extracted with benzene and the insoluble portion chromatographed in ether on Celite buffered at pH 7·0. The eluate yielded *p*-hydroxybenzoic acid (sublimation at 100—118°/0·5 mm. and crystallisation from ether–benzene) (5 mg.), m. p. and mixed m. p. 210—212° (Found: C, 61·2; H, 4·8. Calc. for $C_7H_6O_3$: C, 60·9; H, 4·4%).

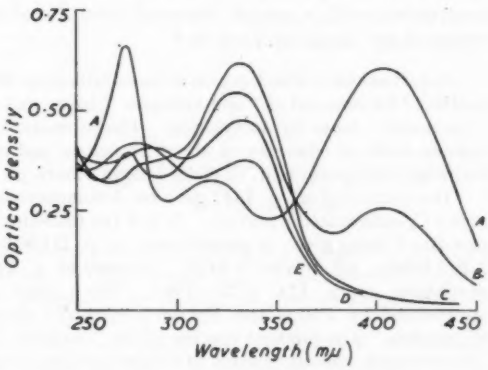
Extract of roots (0·5 *g.*). The acidic fraction of the solute in tubes 35—44 was extracted with hot benzene and the insoluble portion treated with ether. The ethereal solution was

[2] Shaw and Simpson, *J.*, 1955, 655.
[3] Willaman, *J. Amer. Pharm. Assoc.*, 1955, **44**, 408.
[4] Weller, Redemann, Gottshall, Roberts, Lucas, and Sell, *Antibiotics and Chemotherapy*, 1953, **3**, 603.

evaporated, and the pale brown residue (25 mg.) sublimed at 125°/0·1 mm. and crystallised from benzene–acetone, giving fumaric acid (5 mg.), m. p. 288° (sealed tube) (Found: C, 41·6; H, 3·8. Calc. for $C_4H_4O_4$: C, 41·4; H, 3·5%), identified by comparison of the infrared spectra.

Chromatography of the neutral fraction (53 mg.) (tubes 24—34) in benzene on alumina (12 × 1 cm.) and elution with benzene–methanol (99 : 1) gave a solid, m. p. 235—240°, which was sublimed at 200°/10^{-1} mm. and crystallised from ethanol in needles, m. p. 256° (30 mg.; 81 μg/g. fresh wt. of root tissue), identical {mixed m. p. and comparison of the infrared spectra [bands at 3370 and in 3230 cm.$^{-1}$ (OH) and 1649 and 879 cm.$^{-1}$ (>C=CH$_2$)]} with an authentic specimen of betulin (Found, in material dried at 20°: C, 78·3; H, 11·2. Calc. for $C_{30}H_{50}O_2,C_2H_5{\cdot}OH$: C, 78·6; H, 11·55%). The ultraviolet spectrum showed end absorption only. The unit cell of betulin ethanolate was orthorhombic: space group $P2_12_12_1$ or $P2_12_12$; $a = 12{\cdot}64$, $b = 33{\cdot}95$, $c = 7{\cdot}04$ Å; d 1·078; M, 490.

The diacetate (prepared in acetic anhydride–pyridine at 20°) formed prisms, m. p. 218—220°, from ethanol (Found: C, 77·8; H, 10·45. Calc. for $C_{34}H_{54}O_4$: C, 77·5; H, 10·3%).



Decomposition of kaempferol by sodium hydrogen carbonate illustrated by absorption spectra.

A, initial spectrum. *B*, after 22 hr. *C*, after 46 hr. *D*, after 79 hr. *E*, after 219 hr.

The infrared spectrum showed no OH absorption and bands at 1739 (ester C=O) and 1645 and 883 cm.$^{-1}$ (>C=CH$_2$). The unit cell was orthorhombic; space group $P2_12_12_1$ or $P2_12_12$; $a = 15{\cdot}65$, $b = 15{\cdot}82$, $c = 12{\cdot}59$ Å; d 1·125; M, 528. These values give $a : b : c =$ 0·9893 : 1 : 0·7958; Machatschki [5] gave 0·99165 : 1 : 0·7983.

Decomposition of kaempferol by sodium hydrogen carbonate. (*a*) Kaempferol (2·4 mg.), in ethanol (5 ml.), water (10 ml.), and saturated sodium hydrogen carbonate solution (15 ml.), was stored at 20° with occasional shaking and the absorption spectrum between 250 and 450 mμ determined ($l = 0{\cdot}1$ cm.) at intervals up to 220 hr. Optical densities are plotted against wavelength in the Figure. (*b*) Kaempferol 25 mg.) was dissolved in ethanolic sodium hydrogen carbonate as described above; after 240 hr. at 20° ethanol was removed *in vacuo* at 25° and the solution was acidified (concentrated hydrochloric acid) and extracted with ether. Sublimation at 150°/10^{-4} mm. of the gummy extract and crystallisation from ether–benzene gave *p*-hydroxybenzoic acid (6 mg.), m. p. and mixed m. p. 208—210°.

We are indebted to Dr. E. C. Bate-Smith and Dr. T. G. Halsall for gifts of specimens, to Mr. H. G. Hemming for the biological assays, to Dr. P. G. Owston and Miss J. M. Tolliday for the *X*-ray data, and to Mr. S. C. Bishop for technical assistance.

AKERS RESEARCH LABORATORIES, IMPERIAL CHEMICAL INDUSTRIES LIMITED,
THE FRYTHE, WELWYN, HERTS. [*Received, September 10th*, 1957.]

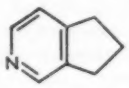
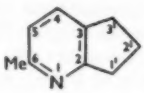
[5] Machatschki, *Z. Krist.*, 1923, **59**, 209.

XUM

339. *Three New Coal-tar Bases.*

By P. Arnall.

A previous communication [1] reported the discovery of 2 : 3-*cyclo*pentenopyridine in vertical-retort coal-tar bases. A higher-boiling fraction has now yielded 3 : 4-*cyclo*pentenopyridine (I), 6-methyl-2 : 3-*cyclo*pentenopyridine (II), and 3 : 4 : 5-trimethylpyridine. Of these the first two are isolated for the first time from natural sources. 3 : 4 : 5-Trimethylpyridine has long been the elusive isomer although its preparation for comparison with a sample obtained from " coal-tar bases from low-temperature coke " is reported by Japanese workers.[2]

(I)  (II) 

Experimental.—The fraction of bases boiling at 209—212° was treated by Perrin and Bailey's method [3] for removal of " non-aromatic " bases, and the primary amines were removed from the " aromatic " bases by acetylation. The aromatic bases were distilled through a fractionating column with an efficiency of about 70 plates, and selected fractions were blended and treated stepwise with picric acid, to yield, among others, picrates of m. p. 144°, 155°, and 178°.

The picrate of m. p. 144° gave on decomposition a base, which from its equivalent weight was a C_3-substituted pyridine. It had the following characteristics, those of 3 : 4-*cyclo*pentenopyridine [4] being given in parentheses: b. p. 211·8°/759 mm. (100°/10 mm.); d_{20}^{20} 1·045, d_4^{20} 1·042 (d_4^{20} 1·0385); n_D^{20} 1·5439 (1·5415); picrate, m. p. 144° (144°); picrolonate m. p. 229° (221°); styphnate, m. p. 174° (175—176°). The picrate of a sample of 3 : 4-*cyclo*pentenopyridine synthesised by Prelog and Metzler's method,[4] when mixed with our picrate, gave no m. p. depression. The infrared spectra of the " natural " and the synthetic material were identical. The retention volume relative to that of pyridine determined on Silicone M. 430 at 160° was 9·9.

The picrate of m. p. 155° gave a solid C_4-substituted pyridine. Its abnormally high density and refractive index indicated that it was not a simple pyridine homologue but contained a condensed ring system and would therefore be a homologue of 2 : 3-*cyclo*pentenopyridine (homologues of 3 : 4-*cyclo*pentenopyridine are excluded, as are also 5 : 6 : 7 : 8-tetrahydroquinoline and -*iso*quinoline, because of their higher b. p.s). The only one described is the 6-methyl derivative, the b. p. of which, given by Basu,[5] is lower than that of ours. Our base had f. p. 31·8°, b. p. 211·9°/761 mm. (Basu gave 195—196°/750 mm.), d_{20}^{23} 0·9910, $n_D^{22\cdot5}$ 1·5297, and gave a picrate, m. p. 155° (Basu gave 151—152°), picrolonate, m. p. 170° (decomp.), and styphnate, m. p. 138—139°. That the methyl group is in the 6- or 1′-position is shown by the facts that these compounds would be the lowest-boiling homologues and that a gas–liquid partition chromatogram on glycerol–kieselguhr shows the base to have a lower retention volume

Relative retention volumes (*pyridine* = 1).

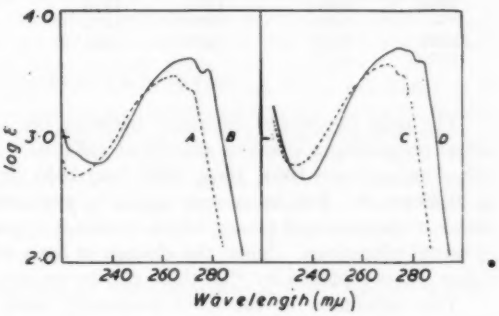
	Glycerol (90°)	Silicone M. 430 (160°)
2 : 3-*cyclo*Pentenopyridine	7·3	7·8
Base of picrate, m. p. 155°	5·5	10·8

(see Table) than 2 : 3-*cyclo*pentenopyridine, behaviour which is expected for 2- and 6-substituted pyridines [6] and expected for 6- and 1′-substituted 2 : 3-*cyclo*pentenopyridines. The 6-position of the methyl group is confirmed by reaction of the methiodide with *p*-dimethylaminobenzaldehyde in methanol,[7] which could not happen if the *cyclo*penteno-group were substituted in the

[1] Arnall, *J.*, 1954, 4040.
[2] Tsuda, Mishima, and Maruyama, *Pharm. Bull.*, 1953, **1**, 283 (*Chem. Abs.*, 1955, **49**, 8277); Ikekawa, Sato, and Maeda, *ibid.*, 1954, **2**, 205 (*Chem. Abs.*, 1956, **50**, 944).
[3] Perrin and Bailey, *J. Amer. Chem. Soc.*, 1933, **55**, 4136.
[4] Prelog and Metzler, *Helv. Chim. Acta*, 1946, **29**, 1170.
[5] Basu, *Science and Culture*, 1937, **2**, 466; *Annalen*, 1937, **530**, 140.
[6] Brooks and Collins, *Chem. and Ind.*, 1956, 1021.
[7] Phillips, *J. Org. Chem.*, 1949, **14**, 302.

1′-position. Further, the ultraviolet spectrum (in *cyclo*hexane; Unicam S.P. 500 spectrophotometer) of the base has the same similarity to the spectrum of 2 : 3 : 6-trimethylpyridine as the spectrum of 2 : 3-*cyclo*pentenopyridine has to that of 2 : 3-dimethylpyridine (see Figure).

The picrate of m. p. 178° gave a solid C_2-substituted pyridine which could not be an ethylmethylpyridine since the highest-boiling of these, 3-ethyl-4-methylpyridine, has b. p. 198°/760 mm.[8] It therefore appears to be 3 : 4 : 5-trimethylpyridine: its properties, compared with published data,[2] are f. p. 36·8° (−), b. p. 211·4—1·5°/759 mm. (205—207°), d_{20}^{40} 0·9471 (d^{15} 0·9616), n_D^{37} 1·5132 (n_D^{15} 1·5103), and it gives a picrate, m. p. 178° (174°), picrolonate, m. p. 232° (decomp.) (188°), and styphnate, m. p. 180° (−). Presence of a 2- or 4-methyl group was indicated by reaction of its methiodide with *p*-dimethylaminobenzaldehyde;[7] ability to prevent



A, 2 : 3-*Dimethylpyridine.*
B, 2 : 3-cyclo*Pentenopyridine.*
C, 2 : 3 : 6-*Trimethylpyridine.*
D, 6-*Methyl* 2 : 3-cyclo*pentenopyridine.*

the formation of a colour between trisodium pentacyanoamminoferrate and dimethyl-*p*-nitrosoaniline showed the absence of a 2-methyl group.[9] The theoretical b. p., calculated by Eguchi's method,[10] is 211°. The relative retention volumes of the base on Silicone M. 450 at 160° and glycerol at 90° are 8·3 and 9·9 respectively (pyridine = 1).

Copies of the infrared spectra of these bases, determined on a Unicam S.P. 100 spectrophotometer, have been submitted for inclusion in the Anglo-German Molecular Spectra Documentation System.[11]

The author thanks Dr. E. R. Wallsgrove for his encouragement, Mr. J. D. Earle for assistance with the experimental work, Dr. V. T. Brooks for gas–liquid partition chromatograms, Mr. D. D. Shrewsbury and Miss C. Wale for infrared and ultraviolet spectra respectively, and the Directors of The Midland Tar Distillers Ltd. for permission to publish this note.

The Midland Tar Distillers Limited, Research Department,
Four Ashes, nr. Wolverhampton. [*Received, September 16th*, 1957.]

[8] Ruzicka and Fornasir, *Helv. Chim. Acta*, 1919, **2**, 338.
[9] Biddiscombe and Herington, *Analyst*, 1956, **81**, 711.
[10] Eguchi, *Bull. Chem. Soc. Japan*, 1928, **3**, 240.
[11] Thompson, *J.*, 1955, 4501.

340. *The Isotope Effect of* ^{18}O *on the Infrared Spectrum of Benzophenone.*

By M. Halmann and S. Pinchas.

Although considerable experimental work has been done on the isotope effect of deuterium on the infrared spectrum of various compounds, there is almost no mention in the literature about the effect of ^{18}O. Only recently it was found by Braude and Turner[1] that the C=^{18}O band of labelled cinnamyl *p*-nitrobenzoate appears at about 1700 cm.$^{-1}$, to be compared with 1730 cm.$^{-1}$ for the unlabelled ester. The highest ^{18}O concentration in the ester measured by them was however only 4·8% and no measurements in other regions

[1] Braude and Turner, *Chem. and Ind.*, 1955, 1223.

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of the infrared spectrum were reported. The infrared absorption of ^{18}O-labelled compounds can be of value as a simple and direct method for the estimation of the content of ^{18}O in all carbonyl compounds: it is also interesting in connection with the assignment of vibrations in various oxygen-containing compounds. Using water containing 83 atoms % of ^{18}O, we have synthesized benzophenone containing 76% of ^{18}O and have measured its infrared spectrum in the 3700—830 cm.$^{-1}$ region (see Table).

The major infrared bands (cm.$^{-1}$) of [^{16}O] and [^{18}O]-benzophenone.

$Ph_2C^{16}O$	$Ph_2C^{18}O$	$Ph_2C^{16}O$	$Ph_2C^{18}O$	$Ph_2C^{16}O$	$Ph_2C^{18}O$	$Ph_2C^{16}O$	$Ph_2C^{18}O$
3070	3065	1449	1449	1178	1178	1002	1002
1664	1663 [a]	1316	1316	1152	1151	973	974
—	1635	1277	1275	1076	1075	940	940
1599	1599	1259 [b]	1259 [b]	1031	1030	919	919
1579	1575						

[a] Shoulder due to residual $C^{16}O$. [b] Shoulder.

The only significant difference between the spectra is in the C=O stretching region where normal benzophenone absorbs at 1664 cm.$^{-1}$ (Depireux [2] gives the value of 1666 cm.$^{-1}$; other values [3] are 1664, 1663, 1662, and 1665 cm.$^{-1}$), whereas ^{18}O-benzophenone absorbs at 1635 cm.$^{-1}$. This behaviour might be expected because of the relatively strong inner bond of the carbonyl group, which makes it appear as one vibrating unit with respect to external vibrations. Since the change in mass of the carbonyl group is relatively small when ^{16}O is replaced by ^{18}O, there can be no considerable difference in these frequencies.

The difference in the C=O frequency when ^{18}O is introduced into benzophenone (29 cm.$^{-1}$) is almost the same as that observed by Braude and Turner [1] (30 cm.$^{-1}$). If one looks at the C=O group and calculates the difference according to Hooke's law using the equation $\nu = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}}$ where ν = wave number (cm.$^{-1}$), c = velocity of light, k = force constant, and μ = reduced mass (assuming the k to be the same in both cases), the following expression is obtained for the ratio of the absorption frequencies:

$$\nu(C=^{18}O)/\nu(C=^{16}O) = \sqrt{[\mu(C=^{18}O)/\mu(C=^{16}O)]} = \sqrt{[(12 \times 16 \times 30)/(28 \times 12 \times 18)]} = 0{\cdot}9759$$

and the isotope shift $\Delta\nu = 1664(1 - 0{\cdot}9759) = 40$ cm.$^{-1}$. This value is in fair agreement with the experimental result. The molecular extinction coefficient of the 1635 cm.$^{-1}$ band of [^{18}O]benzophenone was found to be somewhat smaller than that of the 1664 cm.$^{-1}$ band of normal benzophenone.

Experimental.—The labelled benzophenone [4] was prepared by refluxing dichlorodiphenylmethane [5] [b. p. 107—113°/0·5 mm. (Found: Cl, 30·3. Calc. for $C_{13}H_{10}Cl_2$: Cl, 30·0%), made from normal benzophenone and phosphorus pentachloride (2·466 g.) with water [6] (0·493 g.) containing 83·5 atoms % of ^{18}O for 3 hr. The excess of water was then vacuum-distilled into a trap cooled with liquid air. The remaining oil crystallised, yielding [^{18}O]-benzophenone (1·81 g.). This was recrystallised [4] once from trimethylpentane and twice from *n*-hexane, yielding a ketone (1·48 g.), m. p. 47·5°. The ^{18}O content was determined by Rittenberg and Ponticorvo's method [7] by sealing 63 mg. with 59 mg. of mercuric chloride in an evacuated break-seal tube. After 4 hr. at 425°, the resulting gas was purified with 5 : 6-benzoquinoline [7] (British Drug Houses reagent) and was distilled from a trap cooled in solid

[2] Depireux, *Bull. Soc. chim. belges*, 1957, **66**, 218.
[3] Fuson, Josien, and Shelton, *J. Amer. Chem. Soc.*, 1954, **76**, 2526; Bergmann, Berthier, Ginsburg, Hirshberg, Lavie, Pinchas, Pullman, and Pullman, *Bull. Soc. chim., France*, 1951, **18**, 661; Shigorin, *Doklady Akad. Nauk S.S.S.R.*, 1954, **96**, 769; *Chem. Abs.*, 1954, **48**, 11,191; Thompson, Needham, and Jameson, *Spectrochim. Acta*, 1957, **9**, 208.
[4] Von Doering and Dorfman, *J. Amer. Chem. Soc.*, 1953, **75**, 5595.
[5] Gattermann and Schulze, *Ber.*, 1896, **29**, 2944.
[6] From the separation plant of the Weizmann Institute of Science.
[7] Rittenberg and Ponticorvo, *Internat. J. Appl. Radiation Isotopes*, 1956, **1**, 208.

carbon dioxide into a liquid-nitrogen trap. The ^{18}O content of the carbon dioxide was measured with a Consolidated Engineering Corporation Model 21—401 mass spectrometer, by scanning the masses 44—48. The atom % of ^{18}O was calculated from the peak heights p^X of the masses X:

$$^{18}O(\%) = \frac{100\,(p^{46} + p^{47} + 2p^{48})}{2(p^{44} + p^{45} + p^{46} + p^{47} + p^{48})}$$

The sample measured contained 76·4 atoms % of ^{18}O. In a duplicate sample, 76·0% was measured.

The infrared spectrum of [^{18}O]benzophenone was measured in a carbon tetrachloride solution (0·08 g. in 1 ml.) in a 0·1 mm. cell, on a Perkin-Elmer Model 12C spectrophotometer equipped with a sodium chloride prism. A carbon tetrachloride solution of normal benzophenone was measured at the same time and the calibration of the instrument was checked immediately afterwards with the aid of the water-vapour bands.

The molecular extinction coefficient of the $C=^{18}O$ band at 1635 cm.$^{-1}$ was calculated from the observed optical density of 0·42 for a solution in carbon tetrachloride (32 g./l.) in a 0·01 cm. cell. At this frequency the optical density of the remaining 24% of normal benzophenone was calculated to be 0·02. Hence $\varepsilon(C=^{18}O) = (0{\cdot}40 \times 184 \times 100)/(32 \times 0{\cdot}01 \times 76) = 300$ l. mole^{-1} cm.$^{-1}$. The optical density of a carbon tetrachloride solution (42 g./l.) of normal benzophenone at 1664 cm.$^{-1}$ in the same cell (slit-width in both cases, 0·09 mm.) is 0·84. Therefore $\varepsilon(C=^{16}O) = (0{\cdot}84 \times 182)/(42 \times 0{\cdot}01) = 360$ l. mole^{-1} cm.$^{-1}$. The difference between the values is no doubt larger than the experimental error.

The authors thank Dr. I. Dostrovsky for helpful discussions and Mrs. P. Gueron for mass-spectrometric measurements.

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[*Received, October 28th*, 1957.]

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341. *The Effect of the Salt* Ph_3CSnCl_5 *on the Stannic Chloride-catalysed Polymerisation of Styrene.*

By T. G. BONNER, J. M. CLAYTON, and (the late) GWYN WILLIAMS.

INVESTIGATION of the polymerisation of styrene by stannic chloride in carbon tetrachloride with conditions and concentrations similar to those previously employed [1] has shown that in the presence of a trace of the (triphenylmethyl)tin pentachloride, Ph_3CSnCl_5, the polymerisation is retarded for some hours, though the reaction later occurs at approximately the same rate as for untreated reaction mixture and with formation of a similar product. The salt Ph_3CSnCl_5 is extremely sparingly soluble in carbon tetrachloride and is precipitated as golden-yellow crystals when solutions of triphenylmethyl chloride and stannic chloride in this solvent are mixed. No absorption at 4350 Å characteristic of the Ph_3C^+ ion was apparent in the carbon tetrachloride solution, although in ethylene dichloride, in which this salt is very soluble, there was a marked absorption at this wavelength corresponding to *ca.* 10% ionisation when the concentration of salt was *ca.* 10^{-4}M. In the presence of the solid salt a slow polymerisation at a constant rate is maintained throughout the reaction in carbon tetrachloride, which indicates initiation at the solid surface only, presumably by the Ph_3C^+ ions. When the amount of triphenylmethyl chloride added to the reaction mixture was in excess of that required to remove all of the stannic chloride present as Ph_3CSnCl_5 no polymerisation occurred although the solid salt precipitated was allowed to remain in contact with the styrene solution. This suggests that styrene reacts only through a monomer–catalyst complex.[2]

In a mixed solvent containing 70% of ethylene dichloride, and in pure ethylene dichloride, the pentachloride can be employed in concentrations of the same order as that of the stannic

[1] Williams, *J.*, 1938, 246, 1046; *J.*, 1940, 775.
[2] Plesch, *J. Appl. Chem.*, 1951, **1**, 269; Pepper, *Quart. Rev.*, 1954, **8**, 88.

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chloride (*ca.* 0·015M). Polymerisation is much faster than in pure carbon tetrachloride and monomer begins to disappear rapidly as soon as the reactants are mixed, both when stannic chloride is present alone and when it is in excess over the pentachloride; when the latter only was added to the styrene solution, a slow reaction preceded the rapid reaction in both solvents. The weight of polymer recovered from the pure ethylene dichloride solutions by precipitation with methyl alcohol exceeded the amount of monomer consumed and indicated incorporation of the triphenylmethyl group in the polymer. In both retardations, the colour of the solution due to the Ph_3C^+ ion (orange in the mixed solvent, red in pure ethylene dichloride) faded gradually during the slow stage.

It has been shown previously [3] that triphenylmethyl chloride initiates polymerisation of alkyl vinyl ethers in strongly ionising solvents, while its retarding effect has been reported in the polymerisation of styrene by sulphuric acid in ethylene dichloride.[4] The present work confirms this dual function of triphenylmethyl chloride in the form of its stannic chloride salt but further investigation is needed particularly on the molecular-weight range of the polymeric product to establish to what extent it acts as a chain-breaker as well as a co-catalyst.[4]

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ENGLEFIELD GREEN, SURREY. [*Received, November 6th*, 1957.]

[3] Eley and Richards, *Trans. Faraday Soc.*, 1949, **45**, 436.
[4] Jenkinson and Pepper, *Chem. and Ind.*, 1955, 741.

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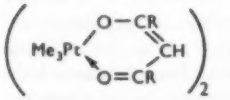
342. *Chelate Derivatives of Trimethylplatinum.*

By A. K. CHATTERJEE, R. C. MENZIES, J. R. STEEL, and F. N. YOUDALE.

TRIMETHYLPLATINUM–ACETYLACETONE was first described in 1928,[1] and trimethylplatinum–dipropionylmethane in 1932.[2] Similar stable, dimeric chelate derivatives of di-*n*- and di-*iso*-butyrylmethane, of di-*n*- and di-*iso*-valerylmethane, and of di-*n*-hexanoylmethane are now described. The double molecular weights in benzene of all these compounds confirm the stable six-covalency of quadrivalent platinum in its trimethyl derivatives already discussed.[3] The more obvious physical characteristics of compounds of the metal are changed by methylation to those of a lower group, but the less obvious, but fundamental co-ordination number remains unchanged.

In this paper attention is rather directed to the changes of properties conditioned by changing the substituents R attached to the stable chelate ring formed by the acetylacetone residue in the structural formula (I). Like trimethylplatinum–acetylacetone, these compounds can all be prepared by heating in benzene or in light petroleum equivalent weights of trimethylplatinum iodide, thallous ethoxide, and the relative β-diketone. Owing to its more sparing, but still convenient, solubility, trimethylplatinum–acetylacetone is the easiest to prepare. The derivatives of the higher diketones can then, as shown in Table 2, be made in good yield by heating it on a water-bath in an open basin with excess of the higher diketone.



(I)

These chelate derivatives of trimethylplatinum, like dimethyl- and diethyl-gold–acetylacetones [4, 5] and the chelate compounds of thallium dialkyls,[6] are white crystalline solids, soluble in organic solvents. The trimethylplatinum derivatives of acetylacetone, of dipropionylmethane, of di*iso*butyrylmethane and of di*iso*valerylmethane decompose without melting at 200°, 190°, 190°, and 156°; that of di-*n*-valerylmethane melts at 160° with

[1] Menzies, *J.*, 1928, 565.
[2] Menzies and Wiltshire, *J.*, 1933, 21.
[3] Lile and Menzies, *J.*, 1949, 1169.
[4] Brain and Gibson, *J.*, 1939, 762.
[5] Gibson and Simonsen, *J.*, 1930, 2532.
[6] Menzies, Sidgwick, Cutliffe, and Fox, *J.*, 1928, 1288.

decomposition. The di-*n*-butyrylmethane and di-*n*-hexanoylmethane derivatives alone have definite melting points at 164—166° and 68—69°. Their molecular weights, determined in boiling benzene, are given in Table 1 as are also their molecular complexities, melting points, and volatilities. Trimethylplatinum–di-*n*-butyrylmethane, –di*iso*butyrylmethane, and –di-*n*-hexanoylmethane all sublimed unchanged in a molecular still. The

TABLE 1.

R in $Me_3Pt(R{\cdot}CO{\cdot}CH{\cdot}COR)$	Volatility	*M*	Complexity
CH_3	160°/20 mm.	648·5	1·91
C_2H_5	105°/0·05 mm.	698	1·902
n-C_3H_7	110°/0·05 mm.	752·5	1·904
iso-C_3H_7	110°/0·05 mm.	732	1·853
n-C_4H_9	135°/0·01 mm.	808	1·91
iso-C_4H_9	140°/0·05 mm.	805·5	1·904
n-C_5H_{11}	120°/0·05 mm.*	862	1·91

* See below.

di*iso*valerylmethane derivative showed distinct tendency to distil at 120°/0·05 mm., but with appreciable decomposition. Table 1 shows that all the compounds were dimeric in boiling benzene, no change of complexity appearing in the range of concentration studied.

The molecular-weight determinations confirm previous results [1,2] in freezing benzene on the acetylacetone and dipropionylmethane compounds of trimethylplatinum. The corresponding thallium compounds show decrease of association with dilution.[7] The greater stability and invariable double molecular weights of the trimethylplatinum compounds are probably related to the stability of the compounds of trimethylplatinum iodide with ammonia,[10] with pyridine,[3] and with ethylenediamine,[3,12] while [13] the dialkylthallium halides can be recrystallised from these liquids and recovered on cooling without solvent of crystallisation. The dialkylgold halides also form compounds with nitrogenous bases, but the molecular weights of dimethyl- and diethyl-gold–acetylacetones have yet to be determined.

The general conditions of stability of the metallic acetylacetone derivatives were discussed by Morgan and Moss.[8,9]

Experimental.—Weighed quantities of trimethylplatinum–acetylacetone [1] were heated in an open basin on a water-bath at 100° to constant weight, with excess of each of the higher diketones, prepared by Adams and Hauser's method.[14] Yields and analyses are given in Table 2, col. 3 recording the weight (g.) of $Me_3Pt(Me{\cdot}CO{\cdot}CH{\cdot}COMe)$ taken, and col. 4 the yield (g.) of $Me_3Pt(R{\cdot}CO{\cdot}CH{\cdot}COR)$.

TABLE 2

R	$R{\cdot}CO{\cdot}CH_2{\cdot}COR$ taken (g.)			Found (%) Pt	C	H	Required (%) Pt	C	H
C_2H_5	1·20	1·65	1·71	52·8	32·8	5·55	53·1	32·7	5·5
C_3H_7	1·25	1·84	2·0	49·6	36·7	6·0	49·35	36·4	6·1
iso-C_3H_7	1·15	1·20	1·30	49·9	36·5	6·3	49·35	36·4	6·1
n-C_4H_9	3·10	2·33	2·12	46·0	39·7	6·7	46·1	39·7	6·7
iso-C_4H_9	1·24	1·12	1·26	—	39·8	6·7	—	39·7	6·7
n-C_5H_{11}	1·41	1·50	1·85	—	42·6	7·1	—	42·55	7·1

Platinum was determined by heating the compound, covered with iodine, in a crucible and after addition of a little chloroform, very slowly and finally to a red heat.[10] Some carbon and

[7] Menzies and Wiltshire, *J.*, 1932, 2734.
[8] Morgan and Moss, *J.*, 1913, **103**, 81.
[9] *Idem*, *J.*, 1914, **105**, 189.
[10] Pope and Peachey, *J.*, 1909, 571.
[11] Foss and Gibson, *J.*, 1951, 299.
[12] Truter and Cox, *J.*, 1956, 948.
[13] Lile and Menzies, *J.*, 1950, 618.
[14] Adams and Hauser, *J. Amer. Chem. Soc.*, 1944, **66**, 1220.

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hydrogen estimations were by the analytical department of the Imperial College of Science and Technology.

As explained above, once trimethylplatinum–acetylacetone has been obtained, the higher derivatives are most conveniently made by metathesis. The application of the thallium method will be clear from the following description.

*Trimethylplatinum–di-*n- *and –di-*iso*-butyrylmethane.* In two separate preparations, di-*n*-butyryl- or di-*iso*-butyryl-methane was mixed with the equivalent (0·005 mole) of thallous ethoxide and trimethylplatinum iodide in toluene, in which all are soluble, and the solution was boiled for 10 min.

The thallous iodide was filtered off, and the toluene removed by boiling with water which acts on the trimethylplatinum derivatives only slowly, and in which they do not dissolve, but which decomposes any remaining thallium compounds, and dissolves their products of decomposition. The solids then remaining in the water were filtered off, dried, and recrystallised from light petroleum; yield 50—60% before sublimation.

The reaction just described is a particular instance of a method of general application. It resembles Purdie's method for methylating sugars by the use of silver oxide and methyl iodide, and, slightly modified, has been similarly applied.[15, 16]

Supplies of trimethylplatinum iodide were obtained from Messrs. Johnson Matthey and Co., whose patient co-operation we appreciate. We also thank Dr. Evans, of the Sondes Place Research Institute, and Professor Wardlaw for their sympathetic interest.

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Sondes Place Research Institute, Dorking, Surrey. [*Received, November 8th*, 1957.]

[15] Fear and Menzies, *J.*, 1926, 937.
[16] Menzies, *J.*, 1947, 1378.

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343. *The Preparation of Tetramethylammonium Hydrogen Dichloride and the Structure of the Hydrogen Dichloride Ion,* HCl_2^-.

By T. C. Waddington.

The existence of halide salts of the organonitrogen bases containing an extra formula unit or more of the hydrogen halide has long been known [1,2] but it was realised only recently [3] that this probably points to the existence of acid halide ions, such as the hydrogen dichloride (bichloride) ion, HCl_2^-.

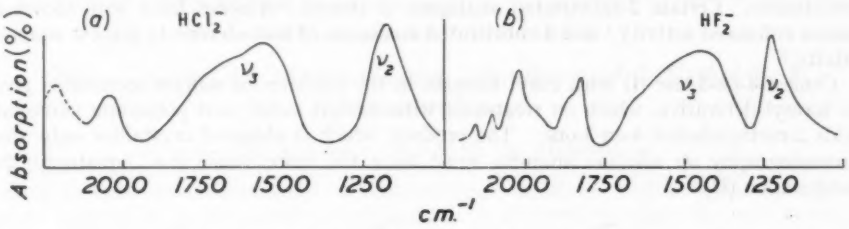
Unlike the hydrogen dichlorides of $(CH_3)_3NH^+$, $(CH_3)_2NH_2^+$, and $CH_3{\cdot}NH_3^+$ which have appreciable vapour pressures at room temperature, that of $(CH_3)_4N^+$ is stable in dry air. The *X*-ray powder photograph of the material $(CH_3)_4N^+HCl_2^-$ showed the existence of a completely new phase. The calculation of the lattice parameters was difficult because of the low crystal symmetry but an orthorhombic unit cell $a = 14{\cdot}81$ Å, $b = 11{\cdot}46$ Å, $c = 10{\cdot}38$ Å, with eight molecules to the unit cell, was assigned, giving a calculated density, $\rho_{calc.}$, of $1{\cdot}09_5$. The observed density, $\rho_{obs.}$, was 1·11.

The infrared spectrum of the solid was compared with that of $(CH_3)_4N^+Cl^-$ in order to identify the contribution of the hydrogen dichloride, HCl_2^-, ion and with that of potassium hydrogen difluoride in order to compare the absorption spectra of the ions HF_2^- and HCl_2^-. The spectrum of the HCl_2^- ion, with the $(CH_3)_4N^+$ peaks omitted, is shown in the Figure (*a*) and that of the HF_2^+ ion in the Figure (*b*).

Only the infrared spectrum of HCl_2^- from 1000 to 3000 cm.$^{-1}$ is shown, although the spectrum was recorded from 400 to 4000 cm.$^{-1}$; no other peaks were found. The spectrum has four features which lead to a tentative assignment. They are: (1) The non-occurrence

[1] McIntosh and Steel, *Proc. Roy. Soc.*, 1904, **73**, 450.
[2] McIntosh and Steel, *Proc. Roy. Soc.*, 1905, **74**, 320.
[3] Herbrandson, Dickerson (jun.), and Weinstein, *J. Amer. Chem. Soc.*, 1952, **76**, 4046.

of the HCl frequency at 2840 cm.$^{-1}$; (2) the occurrence of only two strong infrared bands (at 1180 cm.$^{-1}$ and at 1565 cm.$^{-1}$) in the region 400—4000 cm.$^{-1}$; (3) the enormous displacement of the highest frequency of the HCl_2^- ion (1565 cm.$^{-1}$) from that of the HCl molecule (2840 cm.$^{-1}$); (4) the great similarity, both in shape and position of bands, between the



infrared spectrum of the HCl_2^- ion and the HF_2^- ion,[4] which has been shown to be symmetrical by crystal-entropy [5] and neutron-diffraction [6] studies.

Although the present evidence is insufficient to establish conclusively the structure of the hydrogen dichloride ion, these four points strongly suggest that the ion is linear and that the proton is symmetrically situated, as in the hydrogen difluoride ion. On this basis a tentative assignment of the band at 1180 cm.$^{-1}$ as ν_2 and of the band at 1565 cm.$^{-1}$ as ν_3 is made. Further work is in progress to confirm this assignment and the presence of a symmetric proton.

Experimental.—Tetramethylammonium hydrogen dichloride, $(CH_3)_4N^+HCl_2^-$. Carefully dried hydrogen chloride (1) was passed over pure, dry tetramethylammonium chloride at room temperature, or (2) was condensed on it. The chloride dissolves in liquid hydrogen chloride and when the solution warms much hydrogen chloride is retained above the b. p. of the liquid and comes off at a higher temperature. The compound left at room temperature is the ***hydrogen dichloride*** [Found, from method (1): C, 33·0; H, 9·0; Cl, 48·1%. Found, from method (2): C, 32·2; H, 9·3; Cl, 48·0. $(CH_3)_4N^+HCl_2^-$ requires C, 32·9; H, 9·0; Cl, 48·5%]. Carbon and hydrogen were determined by combustion and chlorine gravimetrically as AgCl.

X-Ray powder photograph. Cu-$K\alpha$ radiation was used. A sample was inserted into a Pyrex capillary by using the " dry box " technique and the capillary was at once sealed with warm picein wax. All the lines on the powder photograph could be indexed on the basis of the assigned orthorhombic cell.

Infrared spectra. Those of $(CH_3)_4N^+HCl_2^-$, $(CH_3)_4N^+Cl^-$, and KHF_2 were taken on a Perkin-Elmer recording infrared, double-beam, spectrophotometer, Model 21, the solids being mulled with Nujol or hexachlorobutadiene in a dry box and smeared between rock-salt plates.

Grateful acknowledgment is made to Dr. N. Sheppard for discussion of the infrared spectra.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 12th*, 1957.]

[4] Coté and Thompson, *Proc. Roy. Soc.*, 1952, *A*, **210**, 206.
[5] Westrum and Pitzer, *J. Amer. Chem. Soc.*, 1949, **71**, 1940.
[6] Patterson and Levy, *J. Chem. Phys.*, 1952, **20**, 704.

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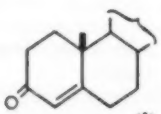
344. *Synthesis of 2α-Methylcholest-4-en-3-one.*

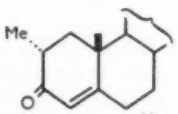
By J. A. K. Quartey.

The synthesis of 2-methylcholest-4-en-3-one was studied as a model for that of 2-methyltestosterone. Certain 2-substituted analogues of steroid hormones have been shown to possess enhanced activity,[1] and 4-substituted analogues of testosterone to possess anabolic activity.[2]

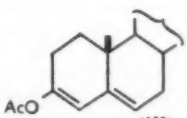
Cholest-4-en-3-one (I) with ethyl formate in the presence of sodium methoxide gives the formyl derivative, which on treatment with methyl iodide and potassium carbonate yields 2-methylcholest-4-en-3-one. The product, which is obtained crystalline only after chromatography on alkaline alumina, must have the more stable (*i.e.*, equatorial) 2α-configuration (II).



(I)



(II)



(III)

An attempt to prepare the 4-methyl compound from the enol acetate (III) by the same method resulted in the 2-substituted derivative. It appears, therefore, that $C_{(2)}$ is the preferred position for reaction,[3] though the heteroannular dienol anion should be formed initially.

By the same general procedure, testosterone has been converted into the 2-formyl derivative and thence 2-methyltestosterone whose properties agree with those reported by Ringold and Rosenkranz.[4] Biological assays carried out by Dr. L. Golberg, of Benger's Ltd., England, show 2-α-methyltestosterone to possess an androgenic : anabolic activity ratio of 0·12 : 0·35 relatively to testosterone.

Since this work was completed, Sondheimer and Mazur [3] have described the preparation of 4-methylcholest-4-en-3-one both *via* the enol lactone and by direct methylation of (I), and Ringold and Rosenkranz [4] have described the preparation of 2α-methyltestosterone *via* the ethoxide.

Experimental.—Formylation of cholest-4-en-3-one. Cholest-4-en-3-one (2·56 g.) was briefly boiled in dry benzene to ensure that it was completely anhydrous, then cooled, and ethyl formate (3·3 c.c.) was added. The mixture was added to sodium methoxide (from 0·92 g. of the metal) suspended in benzene, and the total volume made up with benzene to *ca.* 100 c.c. The mixture was kept at room temperature for 3 days, after which the insoluble sodium salt was filtered off, washed with ether, and decomposed with dilute hydrochloric acid. The formyl compound was then extracted with ether, and the ether extract was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated. 2-Hydroxymethylenecholest-4-en-3-one (2·76 g.) was obtained; crystallised from aqueous acetone it had m. p. 109—110°.

2α-Methylcholest-4-en-3-one. The crude formyl compound (620 mg.) was treated in dry acetone (5 c.c.) with methyl iodide (0·60 c.c.). To the mixture was added freshly ignited potassium carbonate (400 mg.), and after refluxing gently for 24 hr. the mixture was cooled, poured into ether, and washed once with a little water. The ether layer was washed with N-sodium hydroxide until free from acid, then with water and evaporated. The product was dissolved in acetone, and the solution made 0·5N with dilute hydrochloric acid and kept for 24 hr. at room temperature, after which it was poured into ether. The ether layer was washed with water, with dilute aqueous sodium hydroxide (to extract unchanged formyl compound), again with water, dried (Na_2SO_4), and evaporated. The crude product (290 mg.) was chromatographed on alkaline alumina (30 g.; grade 0) and, after a preliminary fraction in benzene,

[1] Hogg, Lincoln, Jackson, and Schneider, *J. Amer. Chem. Soc.*, 1955, **77**, 6401.
[2] Camerino, Patelli, and Vercellone, *ibid.*, 1956, **78**, 3540.
[3] Sondheimer and Mazur, *ibid.*, 1957, **79**, 2906.
[4] Ringold and Rosenkranz, *J. Org. Chem.*, 1956, **21**, 1333.

2α-methylcholest-4-en-3-one was eluted with benzene–ethyl acetate (2 : 1) and crystallised from methanol; it had m. p. 120—122° (Found: C, 84·3; H, 11·6. Calc. for $C_{28}H_{46}O$: C, 84·4; H, 11·6%), $\lambda_{max.}$ 241 mμ (ε 14,000 in ethanol).

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[*Received, November 14th*, 1957.]

345. *5-Alkyl-1 : 2-benzacridines. Synthesis of 5-Methyl-1 : 2-benzacridine.*

By A. CAMPBELL and E. N. MORGAN.

EARLIER syntheses of 5-methyl-1 : 2-benzacridine,[1] like those of 5-methylacridine,[2] possessed drawbacks for large-scale preparations. In attempts to adapt the later synthesis of 5-methylacridine,[3] we found that 5-chloro-1 : 2-benzacridine did not react with diethyl malonate or ethyl cyanoacetate under the usual conditions.

More stringent conditions enabled 5-chloro-1 : 2-benzacridine to react with malononitrile in the presence of sodium butoxide to give 5-dicyanomethyl-1 : 2-benzacridine. Hydrolysis with concentrated sulphuric acid then furnished 5-methyl-1 : 2-benzacridine in good yield. As in the acridine series, 5-methyl-1 : 2-benzacridine was converted by *N*-bromosuccinimide into 5-bromomethyl-1 : 2-benzacridine which with potassium acetate gave 5-acetoxymethyl- and thence 5-hydroxymethyl-1 : 2-benzacridine, and with diethylaminopropylamine gave 5-(3-diethylaminopropylamino)methyl-1 : 2-benzacridine. Ethyl 1 : 2-benzacridine-5-carboxylate [4] was reduced with lithium aluminium hydride to 5-hydroxymethyl-1 : 2-benzacridan. The latter on oxidation with manganese dioxide in benzene at room temperature [5] furnished 5-formyl-1 : 2-benzacridine. This oxidation procedure was also found to be applicable in the acridine series: ethyl acridine-5-carboxylate [6] was reduced to 5-hydroxymethylacridan which, likewise, on treatment with manganese dioxide in benzene furnished 5-formylacridine.

Experimental.—5-Dicyanomethyl-1 : 2-benzacridine. 5-Chloro-1 : 2-benzacridine (26 g.) in xylene (200 c.c.) was added to a solution of sodium butoxide (29·1 g.) and malononitrile (20 g.) in butan-1-ol (750 c.c.), and the mixture refluxed for 16 hr. The butanol and xylene were removed by steam and the residue washed with dilute acetic acid before crystallisation from aqueous dimethylformamide, to give *5-dicyanomethyl-1 : 2-benzacridine* (23 g., 78·5%) in orange platelets, m. p. 310° (Found: C, 81·6; H, 4·1; N, 14·0. $C_{20}H_{11}N_3$ requires C, 81·9; H, 3·8; N, 14·3%).

5-Methyl-1 : 2-benzacridine. 5-Dicyanomethyl-1 : 2-benzacridine (23 g.) was heated in boiling 20N-sulphuric acid (250 c.c.) for 3 hr., the colour of the solution changing from deep orange to yellow-green. After cooling, the mixture was poured into excess of iced aqueous ammonia, and the product filtered off, dried, dissolved in light petroleum (b. p. 60—80°), and passed down a column of activated alumina. Evaporation of the eluate gave 5-methyl-1 : 2-benzacridine (19·4 g., 75·5%), m. p. 125—126°, in very pale yellow prisms.

5-Bromomethyl-1 : 2-benzacridine. 5-Methyl-1 : 2-benzacridine (3·6 g.), *N*-bromosuccinimide (3·6 g.), and benzoyl peroxide (0·5 g.) in carbon tetrachloride (250 c.c.) were refluxed for 4 hr. When cold, the succinimide was filtered off and the filtrate evaporated to small volume under reduced pressure to give *5-bromomethyl-1 : 2-benzacridine* (3·3 g., 69·2%) which recrystallised from carbon tetrachloride in orange prisms, m. p. 194—195° (decomp.) (Found: C, 66·9; H, 3·8; N, 4·3; Br, 24·7. $C_{18}H_{12}NBr$ requires C, 67·0; H, 3·8; N, 4·4; Br, 24·8%).

5-Hydroxymethyl-1 : 2-benzacridine. 5-Bromomethyl-1 : 2-benzacridine (0·5 g.) and potassium acetate (0·5 g.) were refluxed in absolute ethanol (20 c.c.) for 1 hr., then poured into water (100 c.c.). The precipitated product was extracted with ether. Crystallisation of the ether

[1] Postowski and Lundin, *J. Gen. Chem. U.S.S.R.*, 1940, **10**, 71; Buu-Hoï, *J.*, 1949, 670.
[2] Albert, "The Acridines," Edward Arnold, London, 1951, p. 128.
[3] Campbell, Franklin, Morgan, and Tivey, *J.*, 1958, 1145; Morgan and Tivey, B.P. 789,696.
[4] Braun and Wolff, *Ber.*, 1922, **55**, 3675.
[5] Turner, *J. Amer. Chem. Soc.*, 1954, **76**, 5175.
[6] Jensen and Rethwisch, *ibid.*, 1928, **50**, 1144.

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residue from benzene–light petroleum (b. p. 40—60°) gave *5-acetoxymethyl-1 : 2-benzacridine* (0·2 g.) in platelets, m. p. 123—124° (Found: C, 80·0; H, 5·0; N, 4·7. $C_{20}H_{15}O_2N$ requires C, 80·2; H, 5·1; N, 4·9%). This acetate (0·1 g.) was kept in absolute ethanol (10 c.c.), containing N-sodium hydroxide (0·5 c.c.) overnight at room temperature, then poured into water, and the precipitate was collected, dried, and recrystallised from aqueous ethanol, giving pale yellow needles of *5-hydroxymethyl-1 : 2-benzacridine* (50 mg.), m. p. 165—166° (decomp.) (preheated to 160°) (Found: C, 83·0; H, 5·1; N, 5·4. $C_{18}H_{13}ON$ requires C, 83·3; H, 5·0; N, 5·4%).

5-Formyl-1 : 2-benzacridine. A solution of ethyl 1 : 2-benzacridine-5-carboxylate [4] (25 g.) in tetrahydrofuran (200 c.c.) was added dropwise with stirring to ethereal lithium aluminium hydride solution (100 c.c.; 5%) and subsequently refluxed for 2 hr. The cooled mixture was worked up by Micovic and Mihailovic's procedure,[7] to give *5-hydroxymethyl-1 : 2-benzacridan* (18 g.) which recrystallised in pale cream-coloured aggregates, m. p. 148—149° (17 g., 78·4%) (Found: C, 82·4; H, 5·7; N, 5·2. $C_{18}H_{15}ON$ requires C, 82·7; H, 5·8; N, 5·4%). The acridan (16 g.) was shaken in benzene (500 c.c.) with manganese dioxide [5] (40 g.) for 18 hr. After filtration, the benzene residue crystallised from benzene–light petroleum (b. p. 40—60°), to give long needles of *5-formyl-1 : 2-benzacridine* (11 g., 69·8%), m. p. 146—147° (Found: C, 83·9; H, 4·2; N, 5·2. $C_{18}H_{11}ON$ requires C, 84·0; H, 4·3; N, 5·4%).

5-(3-Diethylaminopropylamino)methyl-1 : 2-benzacridine trihydrochloride. 5-Bromomethyl-1 : 2-benzacridine (3·3 g.) and 3-diethylaminopropylamine (10 c.c.) in benzene (100 c.c.) were refluxed for 2 hr. The cooled solution was washed with water, and the benzene evaporated. To the residue in 2N-hydrochloric acid, acetone was added, giving *5-(3-diethylaminopropylamino)-methyl-1 : 2-benzacridine trihydrochloride* in yellow needles (3 g., 62·5%), m. p. 220° (decomp.) (Found: C, 55·9; H, 7·2; N, 8·0. $C_{25}H_{29}N_3,3HCl,3H_2O$ requires C, 56·1; H, 7·2; N, 8·0%).

5-Formylacridine.—Ethyl acridine-5-carboxylate [6] (13 g.) in dry ether (200 c.c.) was added dropwise to a stirred solution of lithium aluminium hydride (10%) in ether (30 c.c.), and the mixture refluxed for 2 hr. Working up [7] gave *5-hydroxymethylacridan* (9 g.), needles [from benzene–light petroleum (b. p. 60—80°)], m. p. 130—131° (decomp.) (Found: C, 79·4; H, 6·3; N, 6·4. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·2; N, 6·6%). Shaking this alcohol (9 g.) in benzene (100 c.c.) overnight at room temperature with manganese dioxide (50 g.), gave 5-formylacridine (7 g.), golden-yellow needles (from aqueous methanol) (6·5 g.), m. p. and mixed m. p. 146—147°.

The authors thank Dr. R. E. Bowman for many helpful discussions.

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STAINES ROAD, HOUNSLOW, MIDDX. [*Received, November 15th*, 1957.]

[7] Micovic and Mihailovic, *J. Org. Chem.*, 1953, **18**, 1192.

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346. *Dodecylquinolinium Bromide.*

By A. V. FEW, A. R. GILBY, R. H. OTTEWILL, and H. C. PARREIRA.

OUR physical [1] and biological [2] work on cationic detergents required dodecyl-trimethyl-ammonium, -pyridinium, and -quinolinium bromide. Reaction of dodecyl bromide with the tertiary base gave the first two bromides directly in a pure state, but the quinoline derivative required wasteful purification. This is a new compound [3] and we record its preparation and some of its properties.

Experimental.—Synthetic quinoline (5 g.) and 1-bromododecane (10 g.) were heated for 5 hr. at 115° in a stream of oxygen-free nitrogen. The reddish solid obtained on cooling was dissolved in 9 : 1 v/v dioxan–acetone at 60°: cooling to 4° gave orange crystals. Fractional recrystallization from dioxan–acetone gave pale yellow crystals of the *salt* (10·6 g.), m. p. 100° (Found: C, 67·0; H, 8·4; N, 4·0; Br, 21·2. $C_{21}H_{32}NBr$ requires C, 66·7; H, 8·2; N, 3·7; Br, 21·2%). This had $\lambda_{max.}$ 2370 and 3160 Å (ε 35,300 and 7450 respectively) in H_2O. A plot

[1] Ottewill and Parreira, unpublished work.
[2] Few and Gilby, unpublished work.
[3] Cf. Schwartz and Perry, "Surface Active Agents," Interscience Publ. Inc., 1949, p. 159.

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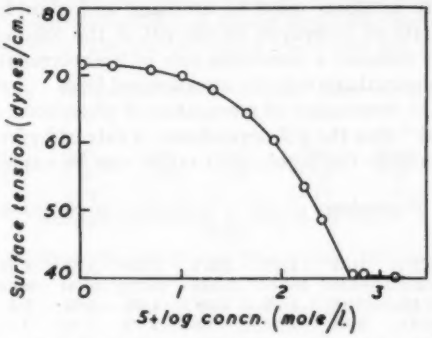
of surface tension against log concentration in water at 25° (drop volume method [4]) is shown in the Figure. Freedom from surface-active impurities was indicated by the absence of a



minimum in the curve at the onset of micelle formation. The critical micelle concentration was $4{\cdot}80 \times 10^{-3}$M.

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[*Received, November* 19*th*, 1957.]

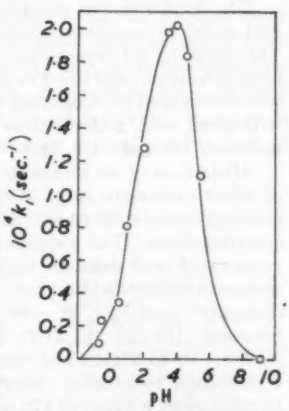
[4] Harkins and Brown, *J. Amer. Chem. Soc.*, 1919, **41**, 499.

347. N-*Phosphourethane*: *Synthesis and Hydrolytic Studies.*

By A. LAPIDOT and M. HALMANN.

ALTHOUGH many amino-derivatives of phosphorus have been synthesized,[1] the only acyl derivative of phosphoramidic acid which has been described [2] is *N*-benzoylphosphoramidic acid, $C_6H_5{\cdot}CO{\cdot}NH{\cdot}PO(OH)_2$. In connexion with studies of the mechanism of carcinogenesis,[3] we prepared *N*-phosphourethane (*N*-ethoxycarbonylphosphoramidic acid; urethane phosphate), $CO_2Et{\cdot}NH{\cdot}PO(OH)_2$, and studied its hydrolysis. It was synthesised by way of an *iso*cyanato-derivative of phosphorus. Recently, Kirsanov [4] described the convenient preparation of phosphoro*iso*cyanatidic dichloride, from which he prepared the acid dichloride of phosphourethane by addition of ethanol to the *iso*cyanate.

In the present work, hydrolysis of this dichloride, $CO_2Et{\cdot}NH{\cdot}POCl_2 + 2H_2O = CO_2Et{\cdot}NH{\cdot}PO(OH)_2 + 2HCl$, was tried under a variety of conditions. (*a*) Hydrolysis in water at room temperature was very slow. (*b*) Hydrolysis in N-sodium hydroxide solution was very rapid and complete; however, difficulties were encountered in removing the inorganic reagents and the water without partially decomposing the phosphourethane. (*c*) Hydrolysis in aqueous dioxan in the presence of silver carbonate was rapid and was the method of choice. Pure phosphourethane is a very hygroscopic, white, crystalline solid. Its acid dissociation constants at 29° are pK_1 2·4 and pK_2 6·3.



Dependence of rate of hydrolysis on pH.

The rate of hydrolysis of phosphourethane in water and in buffer solutions at various ranges of pH was studied. It proceeded with first-order kinetics and was followed by

[1] Kosolapoff, "Organophosphorus Compounds," John Wiley & Sons, Inc., London, 1950.
[2] Titherley and Worral, *J.*, 1909, **95**, 1143.
[3] Haran and Berenblum, *Brit. J. Cancer*, 1956, **10**, 57, giving previous references.
[4] Kirsanov, *Zhur. obshchei Khim.*, 1954, **24**, 1033; *Chem. Abs.*, 1955, **49**, 8787b.

determination of the phosphoric acid produced. No carbon dioxide was released under the conditions of kinetic experiments, as was shown by a separate experiment in aqueous solution. Thus the only products must be urethane and phosphoric acid. Results for the dependence of the rate of hydrolysis on the pH of the solution are given in Table 1 and in the Figure; they indicate a maximum rate of hydrolysis at about pH 4, at which practically all the phosphourethane is in the monoionised form. A similarly high reactivity had been observed for the monoanion of monoesters of phosphoric acid.[5]

It has been suggested [5] that the pH-dependence of rate of hydrolysis of monoalkyl and monoaryl phosphates, outside the highly acid range, can be explained as a unimolecular

TABLE 1. *Dependence of rate of hydrolysis of phosphourethane on* pH.

Temp.	36·3°	37·0°								40·1°	40·1°
Solvent *	$HClO_4$ 5·5N	$HClO_4$ 3·5N	$HClO_4$ 0·35N	HCl 0·11N	HCl 0·01N	KHT 0·03M	KHP 0·05M	A.B. 0·1M	A.B. 0·1M	H_2O	$Na_2B_4O_7$ 0·5M	NaOH 0·1M
pH	—	—	0·45	0·96	1·96	3·58	4·02	4·65	5·4	—	9·07	13
10^4k_1 (sec.$^{-1}$)	0·094	0·23	0·34	0·81	1·28	1·98	2·02	1·83	1·11	0·86	0·0024	0·001

* KHT = potassium hydrogen tartrate; KHP = potassium hydrogen phthalate; A.B. = acetate buffer.

decomposition of the monoanion in the rate-determining step. It seems possible that a similar mechanism occurs in the hydrolysis of phosphourethane:

$$CO_2Et{\cdot}NH{\cdot}PO(OH){\cdot}O^- \xrightarrow{\text{Slow}} CO_2Et{\cdot}NH^- + PO_2{\cdot}OH \xrightarrow[H_2O]{\text{Fast}} CO_2Et{\cdot}NH_2 + PO(OH)_2{\cdot}O^-$$

In a slow stage of heterolysis of the N–P bond, unstable intermediates are formed, which are rapidly hydrated to the products. It is here assumed that metaphosphoric acid is the unstable phosphorus derivative.

Experimental.—Phosphoro*iso*cyanatidic dichloride, prepared according to Kirsanov,[4] had b. p. 20°/5 mm. (Found: Cl, 44·5. Calc. for CO_2NCl_2P: Cl, 44·5%).

The dichloride [4] of phosphourethane was obtained by gradually adding dry ethanol (20 ml., 0·34 mole) to phosphoro*iso*cyanatidic dichloride (58 g., 0·36 mole) with cooling in an ice-bath. The resulting oil crystallized in salt–ice. The crystals, filtered off in the cold, washed with light petroleum, and dried *in vacuo*, had m. p. 20—25° (61·5 g., 82%). Their chlorine content was determined by dissolving a sample in a 10-fold excess of N-sodium hydroxide, neutralization with nitric acid, and titration with standard mercuric nitrate, diphenylcarbazide being used as indicator (Found: Cl, 34·3. Calc. for $C_3H_6O_3NCl_2P$: Cl, 34·5%).

Hydrolysis of the dichloride. This dichloride (6·5 g., 0·027 mole) was added to a suspension of silver carbonate (9 g., 0·033 mole) in aqueous dioxan (1 : 1., 50 ml.) cooled in ice. The reaction was exothermic. Silver chloride was precipitated instantly and was separated by centrifugation. The supernatant liquid was still cloudy; after ordinary filtration it was evaporated and dried in high vacuum, yielding 4·9 g. (91%) of *phosphourethane* (*N-ethoxycarbonylphosphoramidic acid*), a white, powdery, hygroscopic material, which was stored in a desiccator over P_2O_5 at −30°. When heated in a sealed capillary, it melted at about 125° (decomp.) (Found: C, 21·7; H, 5·1; N, 7·8; P, 17·9. $C_3H_8O_5NP$ requires C, 21·3; H, 4·7; N, 8·3; P, 18·3%). The equivalent weight was determined by potentiometric titration with 0·1N-sodium hydroxide. Sharp inflection curves were observed at pH 4·5 and 8·7, corresponding to equivalent weights of 170 and 85 ($C_3H_8O_5NP$ requires 169 and 84·5).

The dissociation constants of phosphourethane were calculated from results of a titration (carried out with a Metrohm AG, Type E148c, pH meter), according to Henderson's formula $pK = -\log (H^+)(B + H^+)/[C - (B + H^+)]$, where H^+ is the hydrogen-ion activity, B is the concentration of sodium hydroxide added, and C is the total concentration of phosphourethane. The average of four determinations gave pK_1 2·4, and the average of three measurements gave pK_2 6·3, both at 29°.

[5] Bailly, *Bull. Soc. chim. France*, 1942, **9**, 421; Desjobert, *ibid.*, 1947, **14**, 809; *Compt. rend.*, 1947, **224**, 575; Vernon, *Proc. Chem. Soc.*, 1957, 136; Butcher and Westheimer, *J. Amer. Chem. Soc.*, 1955, **77**, 2423; Kumamoto and Westheimer, *ibid.*, p. 2515; Chanley and Feageson, *ibid.*, p. 4002; Bernard, Bunton, Llewellyn, Oldham, Silver, and Vernon, *Chem. and Ind.*, 1955, 760.

Kinetics of hydrolysis. Samples of 10—20 mg. of phosphourethane were weighed into 25-ml. volumetric flasks. The appropriate solvent was added, and the flask placed in a thermostat. At intervals, 0·5—2 ml. portions were withdrawn and analyzed for free phosphoric acid by Fiske and Subbarow's method,[6] a Coleman Junior Model 6B Spectrophotometer being used. The low starting values prove that the phosphate itself does not react with the molybdate reagent.

Example of kinetic run: Phosphourethane (initially 3·40 mmoles) in acetate buffer (0·1M; pH 4·65) at 37·0°:

Time (sec.)	0	600	1200	1800	2460	3180	4080	4620	Infinity
H_3PO_4 (mmole) ...	0·32	0·56	0·70	0·86	1·02	1·14	1·36	1·40	2·25
10^4k_1 (sec.$^{-1}$)	—	2·04	1·75	1·75	1·76	1·76	1·83	1·71	—

Average: $k_1 = (1·80 \pm 0·01) \times 10^{-4}$ sec.$^{-1}$.

Test for formation of carbon dioxide during hydrolysis: Nitrogen was bubbled through a solution of phosphourethane (33 mg.) in water (10 ml.) while the temperature was gradually raised from 35° to 80°. No carbon dioxide was detected by barium hydroxide solution in the issuing gas.

The authors are indebted to Professor I. Berenblum for suggesting this problem, and to Dr. D. Rosenthal for valuable comments on the manuscript.

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WEIZMANN INSTITUTE OF SCIENCE, REHOVOTH, ISRAEL. [*Received, November 25th*, 1957.]

[6] Fiske and Subbarow, *J. Biol. Chem.*, 1925, **66**, 375.

348. *Application of the Bruckner Method to the Synthesis of Phenanthridine Derivatives. Part II.*[1]

By T. R. GOVINDACHARI, B. R. PAI, and V. N. SUNDARARAJAN.

THE synthesis of several 1 : 2 : 3 : 4 : 4a : 10a-hexahydro-9-phenylphenanthridines by a modified extension of the Bruckner method [2] was described earlier.[1] In the present work acetyl and phenylacetyl derivatives of the *cis*-2-aryl*cyclo*hexylamines there reported have been prepared and cyclised by phosphorus oxychloride in refluxing toluene to the 9-methyl and the 9-benzyl derivative of 1 : 2 : 3 : 4 : 4a : 10a-hexahydrophenanthridines and then dehydrogenated to the fully aromatic phenanthridines, whose structures in two cases were confirmed by comparison with authentic samples. The ultraviolet absorption maxima of the phenanthridines obtained in this study are tabulated.

Ultraviolet absorption spectra of phenanthridine hydrochlorides in 95% ethanol.

Derivative	$\lambda_{max.}$ (mμ)	log ε
9-Methyl-	250, 330, 345	4·64, 3·37, 3·35
9-Benzyl-	250, 330, 345	4·62, 3·41, 3·28
5 : 9-Dimethyl-	245, 295, 350	4·80, 3·81, 3·35
6(8) : 9-Dimethyl-	250, 295, 330, 345	4·60, 3·66, 3·31, 3·22
7 : 9-Dimethyl-	250, 335, 340, 370	4·64, 3·40, 3·40, 3·01
6-Methoxy-	255, 305, 330	4·68, 4·03, 3·79
6-Methoxy-9-methyl-	230, 255, 308, 325	4·19, 4·57, 3·75, 3·66
9-Benzyl-6-methoxy-	230, 255, 303, 330	4·51, 4·77, 4·02, 3·76
5-Methyl-9-phenyl- (base)	250, 300, 338, 355	4·66, 3·94, 3·43, 3·39

Experimental.—cis-1-*Acetamido*-2-*phenyl*cyclo*hexane*. *cis*-2-Phenyl*cyclo*hexylamine [1] (3 g.), acetic anhydride (9 ml.), and dry pyridine (0·5 ml.) were heated at 100° for 4 hr., then poured into water, and the product (2·4 g.) crystallised from alcohol, giving cis-1-*acetamido*-2-*phenyl*-cyclo*hexane*, m. p. 118—119° (Found: C, 77·0; H, 8·6; N, 6·7. $C_{14}H_{19}ON$ requires C, 77·3; H, 8·8; N, 6·5%).

[1] Part I, Govindachari, Nagarajan, Pai, and Arumugam, *J.*, 1956, 4280.
[2] Bruckner, *Annalen*, 1935, **518**, 227; Bruckner and Kramli, *J. prakt. Chem.*, 1936, **145**, 291; Bruckner, Kiss, and Kovacs, *J.*, 1948, 885; Bruckner and Fodor, *Ber.*, 1943, **76**, 466.

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1 : 2 : 3 : 4 : 4*a* : 10*a*-*Hexahydro*-9-*methylphenanthridine*. A mixture of the acetyl derivative (3 g.) in toluene (75 ml.) and phosphorus oxychloride (15 ml.) was refluxed for 3 hr., cooled, and decomposed with ice. The aqueous layer was made alkaline and extracted with ether. The base in the ethereal layer was purified by one more passage through acid, to give the phenanthridine as an oil (0·4 g.). The *hydrochloride* crystallised from alcohol–ether (m. p. 218—220°) (Found: C, 71·0; H, 8·0; N, 5·6. $C_{14}H_{17}N$,HCl requires C, 71·3; H, 7·7; N, 5·9%); it had $\lambda_{max.}$ 278, 355—375 mμ (log ε 4·01, 2·91).

9-*Methylphenanthridine*. The hexahydrophenanthridine (0·35 g.) was dehydrogenated in *p*-cymene (25 ml.) by 30% palladised charcoal (0·2 g.) during 5 hr. The solution was filtered and extracted with dilute hydrochloric acid. Basification of the acid extract and extraction with ether gave the oily phenanthridine (0·2 g.) whose *hydrochloride*, crystallised from alcohol, had m. p. 282—284° (Found: C, 73·2; H, 5·1. $C_{14}H_{11}N$,HCl requires C, 73·2; H, 5·2%), alone or mixed with the hydrochloride of 9-methylphenanthridine.[3]

9-*Benzylphenanthridine*. *cis*-2-Phenyl*cyclo*hexylamine (3 g.) and phenylacetyl chloride (6 ml.) gave by the Schotten–Baumann method the *phenylacetamide* (2 g.), plates (from methanol), m. p. 149—150° (Found: C, 82·0; H, 7·7; N, 4·5. $C_{20}H_{23}ON$ requires C, 81·9; H, 7·9; N, 4·8%), and thence, by the usual procedure, 9-benzyl-1 : 2 : 3 : 4 : 4*a* : 10*a*-hexahydrophenanthridine (0·35 g. from 3·1 g.) whose yellow *picrate*, m. p. 160—162°, crystallised from alcohol (Found: C, 61·6; H, 4·5. $C_{26}H_{24}N,C_6H_3O_7N_3$ requires C, 61·9; H, 4·8%). Dehydrogenation yielded 9-benzylphenanthridine (0·15 g. from 0·45 g.) whose *hydrochloride* crystallised from alcohol–ether as plates, m. p. 250—252° (Found: C, 78·9; H, 5·3. $C_{20}H_{15}N$,HCl requires C, 78·6; H, 5·2%) alone or mixed with the hydrochloride of 9-benzylphenanthridine.[4]

Similarly were prepared: N-*Acetyl*-cis-2-o-*tolyl*cyclo*hexylamine*, plates (from benzene–light petroleum), m. p. 121—122° (Found: C, 77·6; H, 9·3; N, 6·4. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·2; N, 6·1%); 1 : 2 : 3 : 4 : 4*a* : 10*a*-*hexahydro*-5 : 9-*dimethylphenanthridine hydrochloride* (from alcohol–ether), m. p. 224—226° (Found: C, 71·9; H, 8·0. $C_{15}H_{19}N$,HCl requires C, 72·1; H, 8·1%), $\lambda_{max.}$ 285, 370—380 mμ (log ε 3·98, 2·68); and 5 : 9-*dimethylphenanthridine hydrochloride* (from alcohol–ether), m. p. 256—258° (Found: C, 73·8; H, 6·0. $C_{15}H_{13}N$,HCl requires C, 73·9; H, 5·8%).

5-*Methyl*-9-*phenylphenanthridine* (0·25 g. from 0·35 g. of 1 : 2 : 3 : 4 : 4a : 10a-hexahydro-5-methyl-9-phenylphenanthridine [1]), needles (from light petroleum), m. p. 133—134° (Found: C, 89·2; H, 5·7. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6%).

N-Acetyl-*cis*-2-*m*-tolyl*cyclo*hexylamine, an oil; 1 : 2 : 3 : 4 : 4a : 10a-*hexahydro*-6(8) : 9-*dimethylphenanthridine hydrochloride* (from alcohol–ether), m. p. 210—212° (Found, after drying at 138° for 6 hr.: C, 67·1; H, 8·5. $C_{15}H_{19}N$,HCl,H_2O requires C, 67·3; H, 8·3%), $\lambda_{max.}$ 270, 285 mμ (log ε 3·80, 3·78); and 6(8) : 9-*dimethylphenanthridine hydrochloride* (from alcohol–ether), m. p. 276—278° (Found: C, 74·1; H, 6·1%).

N-*Acetyl*-cis-2-p-*tolyl*cyclo*hexylamine* (from benzene–light petroleum), m. p. 160° (Found: C, 77·7; H, 9·3%); 1 : 2 : 3 : 4 : 4*a* : 10*a*-*hexahydro*-7 : 9-*dimethylphenanthridine hydrochloride* (from alcohol–ether), m. p. 228—230° (Found, after drying at 138° for 6 hr.: C, 66·9; H, 8·0%), $\lambda_{max.}$ 280, 375 mμ (log ε 3·99, 3·30); and 7 : 9-*dimethylphenanthridine hydrochloride*, yellow needles (from alcohol–ether), m. p. 296—298° (Found: C, 73·8; H, 6·0%).

cis-2-(*m*-Methoxyphenyl)*cyclo*hexylamine [1] (2 g.) and 95% formic acid (8 ml.) gave the gummy *N*-formyl derivative and thence 1 : 2 : 3 : 4 : 4*a* : 10*a*-*hexahydro*-6-*methoxyphenanthridine picrate* (from alcohol), m. p. 204° (Found: C, 54·4; H, 4·8; N, 12·8. $C_{14}H_{17}ON,C_6H_3O_7N_3$ requires C, 54·1; H, 4·5; N, 12·6%), and 6-*methoxyphenanthridine hydrochloride*, needles (from alcohol), m. p. 236—238° (Found: C, 68·4; H, 5·2; N, 5·5. $C_{14}H_{11}ON$,HCl requires C, 68·4; H, 4·9; N, 5·7%).

N-*Acetyl* cis-2-(m-*methoxyphenyl*)cyclo*hexylamine*, leaflets (from benzene–light petroleum), m. p. 114—115° (Found: C, 72·9; H, 8·2; N, 6·0. $C_{15}H_{21}O_2N$ requires C, 72·9; H, 8·5; N, 5·7%); 1 : 2 : 3 : 4 : 4a : 10a-*hexahydro*-6-*methoxy*-9-*methylphenanthridine picrate* (from alcohol), m. p. 168° (Found: C, 54·9; H, 4·8; N, 11·7. $C_{15}H_{19}ON,C_6H_3O_7N_3$ requires C, 55·0; H, 4·8; N, 12·2%), and 6-*methoxy*-9-*methylphenanthridine hydrochloride* (from alcohol), m. p. 245° (Found: C, 69·7; H, 5·4; N, 5·7. $C_{15}H_{13}ON$,HCl requires C, 69·4; H, 5·4; N, 5·4%).

cis-2-(*m*-Methoxyphenyl)*cyclo*hexylamine gave the *phenylacetyl derivative* (from benzene–light petroleum), m. p. 114—116° (Found: C, 77·8; H, 7·4; N, 4·4. $C_{21}H_{25}O_2N$ requires C, 78·0; H, 7·7; N, 4·3%), and thence 9-*benzyl*-6-*methoxyphenanthridine hydrochloride*, needles

[3] Morgan and Walls, *J.*, 1931, 2447.
[4] Ritchie, *J. Proc. Roy. Soc., New South Wales*, 1945, **78**, 147; *Chem. Abs.*, 1946, **40**, 877.

(from alcohol), m. p. 262—264° (Found: C, 74·8; H, 5·4. $C_{21}H_{17}ON,HCl$ requires C, 75·1; H, 5·4%).

We thank the Government of Madras for the award of a Research Assistantship (to V. N. S.) and Mr. S. Selvavinayakam for microanalyses.

PRESIDENCY COLLEGE, MADRAS, INDIA. [*Received, November 26th*, 1957.]

349. *Florisil as an Adsorbent for Basic Substances.*

By A. ASATOOR and C. E. DALGLIESH.

THE advantages of adsorption for preliminary separation of groups of compounds from complex mixtures have been outlined.[1,2,3] The synthetic adsorbent Florisil (a magnesia–silica gel: Floridin Company, Tallahassee, Florida) has been used to isolate certain polycyclic molecules, *e.g.*, riboflavin,[4] alkaloids such as morphine, codeine, and heroin,[5] and flavins.[6] We have now found that Florisil is a good general adsorbent for bases, which can subsequently be eluted with high recoveries with pyridine–acetic acid.

Adsorption behaviour on Florisil.

The figures under "filtrate" and "eluate" represent percentage recoveries under the standard experimental conditions. The concentration of adsorbate solution was 0·0005M except where otherwise stated.

Substance	Filtrate	Eluate	Substance	Filtrate	Eluate
		Bases			
Adenine	0	94	Adrenaline	0	96
2-Phenylethylamine	0	98	Tryptamine	0	94
Tyramine	0	95	5-Hydroxytryptamine	0	96
3 : 4-Dihydroxyphenylethylamine	0	92	Histamine	0	94
Noradrenaline	6	92	Codeine	0	100
		Amino-acids			
Glycine	100	0	Thyroxine	95	6
Cystine (0·00025M)	100	0	Tryptophan	97	2
Glutamic acid	100	0	5-Hydroxytryptophan	96	0
Glutamine	100	0	Citrulline	91	6
Asparagine	100	0	Histidine	97	4
Phenylalanine	97	0	Lysine	5	95
Tyrosine	100	0	Arginine	5	96
3 : 4-Dihydroxyphenylalanine	96	1	Ornithine	0	100
		Miscellaneous			
Urea	100	0	Guanine	73	22
Creatinine	100	0	Cytosine	86	15
Uric acid	100	0	Riboflavin (2 mg./l.)	0	80
Anthranilic acid	100	0	Riboflavin (2 mg./l.)	0	95[a]
5-Hydroxyindolylacetic acid	100	0	Xanthopterin	12	81
Glucosamine	93	7	Xanthopterin	0	92[b]
Xanthine	85	15			
		Inorganic ions			
Cl^- [as 0·9% (w/v) NaCl]	100	0	K^+ [as 0·4% (w/v) KCl]	2	95
PO_4^{3-} (as 0·037M-KH_2PO_4)	91	5	Ca^{2+} (as 0·005M-$CaCl_2$)	0	96
Na^+ [as 0·9% (w/v) NaCl]	63	40			

[a] Increased recovery of riboflavin by using 75 ml. of eluant instead of standard 50 ml. [b] Increased adsorption and recovery of xanthopterin by using twice the standard amount of adsorbent.

The results in the Table were obtained by using a standard set of conditions (see Experimental) and are largely self-explanatory. It is noteworthy that basic amino-acids are

[1] Dalgliesh, *J. Clin. Path.*, 1955, **8**, 73.
[2] Asatoor and Dalgliesh, *J.*, 1956, 2291.
[3] *Idem, ibid., J.*, 1958, 1498.
[4] Ferrebee, *J. Clin. Invest.*, 1940, **19**, 251.
[5] Stolman and Stewart, *Analyst*, 1949, **74**, 536.
[6] Dimant, Sanadi, and Huennekens, *J. Amer. Chem. Soc.*, 1952, **74**, 5440.

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readily separated from other amino-acids. Histidine behaves like a non-basic amino-acid, which is compatible with its low isoelectric point (*ca.* 7·6) relative to, say, that of lysine (*ca.* 9·7). The biogenic amines can also be separated from their precursor amino-acids, or non-basic metabolites (cf. 5-hydroxyindolylacetic acid). Glucosamine behaves like a non-basic substance, which is compatible with its unusually low pK_a (7·8; cf. isoelectric point of histidine, 7·6) relative to that of other monoamines (*e.g.*, methylamine, pK_a 10·7). Inorganic cations are also adsorbed and recovered to varying extents. Xanthine, guanine, and cytosine are only partially adsorbed under the standard conditions.

Experimental.—Standard adsorption and elution procedure. Florisil (100—200 mesh; it resembles alumina in its handling properties) was first freed from dust and adsorbed gases by suspending it in 2% (v/v) acetic acid and stirring at intervals for ½ hr.[4] The supernatant liquid was decanted and the granular mass repeatedly washed with water and then poured as a slurry into a glass chromatography tube plugged with glass wool. The column of adsorbent (1½ × 8 cm.) was washed with water and finally a pad of glass wool placed on top. The solution of adsorbate [25 ml. of a solution (usually 0·0005M) previously adjusted to pH 4 with acetic acid] was poured on the column and after adsorption the column was washed with 50 ml. of water. The combined effluent and washings (" Filtrate ") was kept for analysis. The column was then eluted with 50 ml. of a solution of 20% (v/v) pyridine in 2% (v/v) acetic acid, followed by 50 ml. of water. The combined effluent and washings (" Eluate ") was evaporated to dryness under reduced pressure in a water-bath kept below 80°. The dried residue was again taken up in water and re-evaporated to ensure removal of pyridine, and the residue finally dissolved and made up to a known volume. The " filtrate " was similarly evaporated.

Estimation of adsorbates. Riboflavin was estimated fluorimetrically at pH 7 with Laurence's fluorimeter[7]; a Chance blue OB 10 filter was used on the primary (activation) side and an Ilford orange-yellow filter on the secondary (emission) side. Codeine was estimated by measuring its absorption at 284 mμ in 0·1N-hydrochloric acid. Other substances were estimated as previously described.[2,3]

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[*Received, November 29th*, 1957.]

[7] Laurence, *Biochem. J.*, 1957, **65**, 27P.

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350. *The Dimer of* o-*Benzoquinone.*

By JOHN HARLEY-MASON and A. H. LAIRD.

OXIDATION of catechol in ethereal solution with silver oxide has long been known to give *o*-benzoquinone. We have now found that on similar oxidation in acetone solution, *o*-benzoquinone is first formed (and can be isolated by rapid evaporation of the solvent) but that, if the solution is kept, a yellow crystalline dimer soon separates. The dimer, in contrast to *o*-benzoquinone, is stable indefinitely in the solid state.

The structure (I), similar to that proposed by Horner and Sturm[1] for the dimer of 4 : 5-dimethyl-*o*-benzoquinone and formed by a Diels–Alder addition of one molecule of the quinone to another, is proposed for our product on the following grounds. The infrared spectrum showed no hydroxyl peak and no peaks characteristic of a benzene ring. Four carbonyl peaks were present, at 5·69, 5·75, 5·80, and 5·93 μ, the first three corresponding to unconjugated carbonyl groups and the last to a conjugated carbonyl group. In addition a peak at 6·19 μ corresponded to the double bond of the system $-CO\cdot CH{=}CH-$. The ultraviolet spectrum showed a single maximum, at 233 mμ, a wavelength which is too low for any benzenoid compound. When boiled in aqueous solution the dimer was rapidly converted into a more soluble phenolic isomer (II; R = H) which gave an intense green ferric chloride reaction, indicating a catechol nucleus. The infrared spectrum showed sharp peaks at 2·97 (OH) and 6·23 and 6·67 μ (benzene ring), and there was a single ultraviolet maximum at 270 mμ.

[1] Horner and Sturm, *Annalen*, 1955, **597**, 1.

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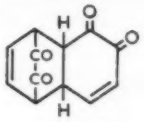
With acetic anhydride, the new isomer gave a diacetyl derivative (II; R = Ac); and with *o*-phenylenediamine a quinoxaline derivative (III), which gave an intense green ferric chloride reaction.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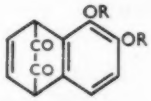
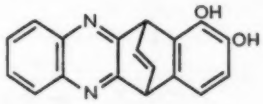

(II)


(III)

This Diels–Alder type of dimerisation appears to take place only in polar but non-hydroxylic organic solvents; *o*-benzoquinone rapidly decomposes in hydroxylic solvents and in water, but in such cases no dimer can be isolated.

Experimental.—o-Benzoquinone dimer. To a solution of catechol (2 g.) in acetone (100 ml.) freshly precipitated silver oxide (8 g.) was added, and the mixture was shaken for 10 min. and then filtered. Overnight the filtrate deposited the *dimer* (0·6—1 g.) as bright yellow plates, which melted partially at 125—130°, then resolidified, and finally melted at 194—195°, probably indicating thermal conversion into the phenolic isomer [Found: C, 66·5; H, 3·8%; *M* (Rast), 189. $C_{12}H_8O_4$ requires C, 66·7; H, 3·7%; *M*, 216].

Boiling the dimer (1 g.) with water (50 ml.) for 5 min. produced an orange solution. This was extracted with ethyl acetate (3 × 30 ml.), the extracts were separated and evaporated to dryness, and the residue was recrystallised from ethyl acetate–light petroleum, giving the phenolic *isomer* (II; R = H) as orange-yellow plates, m. p. 195—196° (Found: C, 66·4; H, 3·8%). The compound was acetylated by boiling acetic anhydride for an hour. The excess of anhydride was removed under reduced pressure and the residue recrystallised from ethyl acetate–light petroleum, giving yellow prisms of the *diacetate* (II; R = Ac), m. p. 144° (Found: C, 63·4; H, 4·0. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0%).

To a solution of *o*-benzoquinone dimer (keto-isomer; 0·359 g.) in boiling ethanol (50 ml.) a solution of *o*-phenylenediamine (0·375 g.) in ethanol (20 ml.) was added. On concentration and cooling, colourless needles of the *quinoxaline derivative* (III) separated; they had m. p. 333° after recrystallisation from ethanol (Found: C, 74·8; H, 3·8; N, 9·6. $C_{18}H_{12}O_2N_2$ requires C, 75·0; H, 4·2; N, 9·7%).

The authors thank Dr. N. Sheppard for valuable discussions of the spectroscopic data.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 29th*, 1957.]

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351. *The Synthesis of 1-Arylarsindolines.*

By EMRYS R. H. JONES, and FREDERICK G. MANN.

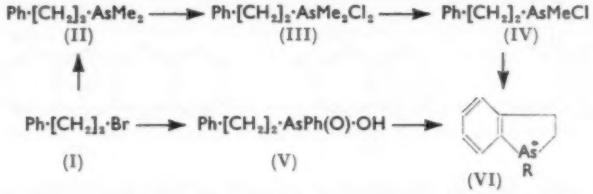
THE first member of the arsindoline series, 1-methylarsindoline (VI; R = Me), was prepared by Turner and Bury,[1] who converted phenethyl bromide (I) into a Grignard reagent, which with iododimethylarsine gave dimethylphenethylarsine (II). This arsine combined directly with chlorine to give the arsine dichloride (III), which when heated afforded methyl chloride and the chloroarsine (IV): cyclisation by using aluminium chloride in carbon disulphide finally gave the methylarsindoline.

We have prepared 1-phenylarsindoline (VI; R = Ph) by a much shorter route, wherein phenethyl bromide (I) is added to dichlorophenylarsine in boiling aqueous sodium hydroxide (the Meyer reaction) to furnish the purified phenethylphenylarsinic acid (V) in 33% yield. This acid is readily cyclised by sulphuric acid to 1-phenylarsindoline oxide, which without isolation is reduced by sulphur dioxide to the arsindoline (VI; R = Ph) in 76% overall yield from the acid (V).

The acid (V) can be reduced by sulphur dioxide and hydrochloric acid to *As*-chloro-*As*-phenethyl-*As*-phenylarsine, $Ph{\cdot}[CH_2]_2{\cdot}AsPhCl$, in 67% yield, but cyclisation of this chloroarsine using aluminium chloride gives the arsindoline (VI; R = Ph) in only 17% yield.

[1] Turner and Bury, *J.*, 1923, **123**, 2489.

It is not known whether this ready cyclisation of arsinic acids of type (V) is limited to those having an aryl group directly linked to the arsenic atom.



Attempted dehydrogenation of the arsindoline (VI; R = Ph) to 1-phenylarsindole, by boiling its xylene solution with tetrachloro-*o*-benzoquinone or its ethylene glycol solution with palladised charcoal, failed; the arsindoline was also largely unaffected when its solution in carbon tetrachloride containing *N*-bromosuccinimide and benzoyl peroxide was boiled for 4 hr. Attempted oxidation of the arsindoline to a 2- or 3-oxo-derivative, by hot aqueous potassium permanganate (cf. Jones and Mann [2]) or by selenium dioxide in hot ethanol, gave mainly the arsine oxide, identified by reduction with sulphur dioxide and then conversion into 1-phenylarsindoline methiodide.

Experimental.—Phenethylphenylarsinic acid (V). Dichlorophenylarsine (90 c.c., 147 g.) was added dropwise to a warm solution of sodium hydroxide (118 g., 4·5 mol.) in water (500 c.c.), to which phenethyl bromide (100 c.c., 135 g., 1 mol.) was then added, and the mixture was boiled for 6 hr. The cold solution was extracted with ether to remove unchanged bromide and was then made just acid (Congo-red) with hydrochloric acid. The *acid* (V) was deposited as an oil which solidified when washed with much cold water and recrystallised from acetone as colourless crystals (63 g., 33%), m. p. 142—143° (Found: C, 58·2; H, 5·3. $C_{14}H_{15}O_2As$ requires C, 57·9; H, 5·2%). Repetition of the experiment on one-tenth of the above scale gave a yield of 47%.

1-*Phenylarsindoline* (VI; R = Ph). A mixture of the acid (V) (20 g.) and concentrated sulphuric acid (100 c.c.) was heated at 100° for 15 min., cooled, poured into water (500 c.c.), and neutralised with 30% aqueous sodium hydroxide. The precipitated oily arsindoline oxide was extracted with chloroform (2 × 75 c.c.), and the united extracts were added to a mixture of concentrated hydrochloric acid (100 c.c.) and water (100 c.c.) containing potassium iodide (0·1 g.), through which sulphur dioxide was then passed for 2 hr. The mixture was set aside overnight, and the chloroform layer, when collected, dried (Na_2SO_4) and distilled, afforded the *arsindoline* (VI; R = Ph) (13·5 g., 76%) as a colourless odourless liquid, b. p. 126—128°/0·6 mm. (Found: C, 65·8; H, 5·4. $C_{14}H_{13}As$ requires C, 65·6; H, 5·1%).

The arsine readily combined with cold methyl iodide, and the product when crystallised from ethanol afforded the colourless *methiodide monohydrate*, m. p. 174—175° (effervescence) (Found: C, 43·3; H, 4·1. $C_{15}H_{16}IAs,H_2O$ requires C, 43·2; H, 4·3%). The oxide and the metho- and etho-bromide were obtained only as gums.

A hot aqueous-ethanolic solution of potassium palladobromide, when treated with the arsindoline (2 mols.), rapidly deposited orange *dibromobis-1-phenylarsindolinepalladium*, m. p. 229—230° (decomp.) (Found: C, 43·1; H, 3·4. $C_{28}H_{26}Br_2As_2Pd$ requires C, 43·1; H, 3·4%). This compound is insoluble in most solvents, but could be recrystallised (without change of m. p.) by adding dioxan dropwise to a boiling ethanolic suspension until a clear solution was obtained.

As-*Chloro*-As-*phenethyl*-As-*phenylarsine*. Sulphur dioxide was passed for 6 hr. through a suspension of the acid (V) (28 g.) in a mixture of concentrated hydrochloric acid (250 c.c.) and water (250 c.c.) containing potassium iodide (0·2 g.). The oily layer, when collected, dried (Na_2SO_4), and distilled gave: (*a*) dichlorophenylarsine (b. p. *ca.* 60°/0·3 mm.); and (*b*) the yellow liquid *chloro-arsine*, b. p. 137—140°/0·3 mm. (18·9 g., 67%) (Found: C, 57·85; H, 4·9. $C_{14}H_{14}ClAs$ requires C, 57·4; H, 4·8%).

A mixture of the chloro-arsine (15·0 g.), powdered aluminium chloride (7 g.), and benzene (50 c.c.) was heated at 100° for 3 hr., although evolution of hydrogen chloride ceased after 15 min. The mixture was poured into dilute hydrochloric acid, warmed gently with stirring,

[2] Emrys R. H. Jones and Mann, *J.*, 1958, 294.

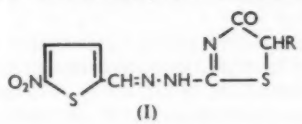
and filtered. The benzene layer, when dried and distilled, gave the fractions: (*a*) b. p. 90—95°/0·5 mm., 2·5 g.; (*b*) the crude arsindoline (VI; R = Ph), b. p. 115—140°/0·5 mm., 2·3 g., 17%. The latter gave the above methiodide, m. p. and mixed m. p. 174° (from ethanol).

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 5th*, 1957.]

352. *Thiophen Derivatives. Part XI.* Substitution in 2-Thenaldehyde.*

By NG. PH. BUU-HOÏ and DENISE LAVIT.

ALTHOUGH nitration of 2-thenaldehyde and its derivatives has often been investigated, the records are confused and at times contradictory. Foye, Hefferen, and Feldmann,[1] treating 2-thenaldehyde with fuming nitric acid in sulphuric acid at low temperature, obtained as sole substitution product 4-nitro-2-thenaldehyde; Gever [2] nitrated 2-thenaldehyde diacetate in acetic anhydride and obtained a eutectic, inseparable mixture of 4- and 5-nitro-2-thenaldehyde, a result similar to that of Rinkes [3] in the nitration of 2-acetylthiophen. Patrick and Emerson,[4] however, using a similar procedure, reported the successful preparation of 5-nitro-2-thenaldehyde, m. p. 75—76°. Campaigne *et al.*[5] prepared the latter aldehyde anew, and recorded m. p. 252—255° for its thiosemicarbazone. It has now been found that nitration of 2-thenaldehyde with fuming nitric acid in acetic anhydride gives mainly 5-nitro-2-thenaldehyde (m. p. 77°), along with some of the 4-isomer, which is eliminated by crystallisation from ethanol. 5-Nitro-2-thenaldehyde thiosemicarbazone was obtained as a yellow product, m. p. 185° (decomp.); its condensation with chloroacetic acid and with higher α-brominated fatty acids yielded the corresponding 5-nitro-2-thenaldehyde 4-oxo-Δ^2-thiazolin-2-ylhydrazones (I). A remarkable feature of the chemistry of 5-nitro-2-thenaldehyde is its failure to react with arylaceto-



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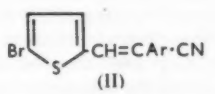

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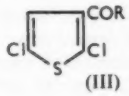

(III)

nitriles in the presence of alkaline catalysts (*e.g.*, piperidine), a reaction which can be effected with a number of thenaldehydes to give the corresponding α-aryl-β-thienylacrylonitriles; [6] attempts to condense 5-nitro-2-thenaldehyde with ethyl malonate and with 2 : 4 : 6-trinitrotoluene in the presence of piperidine were likewise unsuccessful.

2-Thenaldehyde readily underwent monobromination, mainly to 5-bromo-2-thenaldehyde, a liquid (thiosemicarbazone, m. p. 182°), which had previously been prepared by formylation of 2-bromothiophen in the presence of phosphorus oxybromide [7] and by the Sommelet method.[5] Unlike the nitro-aldehyde, 5-bromo-2-thenaldehyde readily condensed with arylacetonitriles to the corresponding α-aryl-β-bromothienylacrylonitriles (II).

These results underline the outstanding reactivity of position 5 in 2-substituted thiophens, even when the substituent is *meta*-directing. The considerably less pronounced reactivity of the 3- and the 4-position is further demonstrated by the relative inertia of 2 : 5-dichlorothiophen in Friedel–Crafts acylations; only poor yields of 3-acyl-2 : 5-dichlorothiophens (III) were recorded when acid chlorides were used, and no normal keto-acid was formed with phthalic anhydride in the presence of aluminium chloride.

* Part X, Buu-Hoï, Lavit, and Xuong, *J.*, 1955, 1581.

[1] Foye, Hefferen, and Feldmann, *J. Amer. Chem. Soc.*, 1954, **76**, 1378.
[2] Gever, *ibid.*, 1955, **77**, 577.
[3] Rinkes, *Rec. Trav. chim.*, 1933, **52**, 538.
[4] Patrick and Emerson, *J. Amer. Chem. Soc.*, 1952, **74**, 1356.
[5] Campaigne, Monroe, Arnwine, and Archer, *ibid.*, 1953, **75**, 988.
[6] Buu-Hoï, Hoán, and Lavit, *J.*, 1950, 2130; 1951, 251; 1952, 4590; Cagniant, *Bull. Soc. chim. France*, 1949, **16**, 850.
[7] Cf. King and Nord, *J. Org. Chem.*, 1948, **13**, 635.

Experimental.—Nitration of 2-thenaldehyde. An ice-cooled solution of 2-thenaldehyde (13 g.; prepared by formylation of thiophen with dimethylformamide and phosphorus oxychloride) in acetic anhydride was treated dropwise with fuming nitric acid (9·9 g.; *d* 1·49) in acetic acid, with stirring. As soon as the first crystals appeared, water was added, and the solid precipitate (14·5 g.) was collected, washed with water, and recrystallised twice from ethanol, giving 5-nitro-2-thenaldehyde as needles, m. p. 77°. Small amounts of 4-nitro-2-thenaldehyde (m. p. 35°) were isolated from the mother-liquors. The semicarbazone formed pale yellow needles, m. p. 269° (decomp.), from acetic acid; Patrick and Emerson [4] gave m. p. 242—243°. The thiosemicarbazone, prepared from the thenaldehyde (9·5 g.) and thiosemicarbazide (5·5 g.) in acetic acid, formed yellow flakes, m. p. 185° (decomp.), from acetic acid.

5-Nitro-2-thenaldehyde 4-oxo-Δ^2-thiazolin-2-ylhydrazone (I; R = H) was formed when the thiosemicarbazone (2·4 g.), chloroacetic acid (0·3 g.), and methanol (30 c.c.) were refluxed for 8 hr. with sodium acetate (0·3 g.), and the precipitate was recrystallised from ethanol, giving yellow needles (0·4 g.), m. p. 289—290° (Found: C, 35·3; H, 2·0. $C_8H_6O_3N_4S_2$ requires C, 35·6; H, 2·2%). The *5-ethyl-4-oxo-Δ^2-thiazolin-2-ylhydrazone* (I; R = Et), similarly prepared from α-bromobutyric acid, formed yellow needles, m. p. 265° (Found: C, 40·0; H, 3·3. $C_{10}H_{10}O_3N_4S_2$ requires C, 40·3; H, 3·4%); the *5-butyl* (I; R = Bu), yellow needles, m. p. 238° (Found: C, 44·0; H, 4·2. $C_{12}H_{14}O_3N_4S_2$ requires C, 44·2; H, 4·3%), *5-pentyl* (I; R = C_5H_{11}), needles, m. p. 228° (Found: C, 45·6; H, 4·5. $C_{13}H_{16}O_3N_4S_2$ requires C, 45·9; H, 4·7%), and *5-tetradecyl analogue* (I; R = $C_{14}H_{29}$), pale yellow needles, m. p. 161° (Found: C, 56·3; H, 7·1. $C_{22}H_{34}O_3N_3S_2$ requires C, 56·6; H, 7·4%), were also prepared.

Bromination of 2-thenaldehyde. To an ice-cooled solution of 2-thenaldehyde (16 g.) in dry chloroform, bromine (22·7 g.) was added dropwise with stirring, and the mixture left at room temperature for 2 hr., then poured into water ; the product was then taken up in chloroform, washed with aqueous sodium carbonate, then with water, and dried (Na_2SO_4), the solvent distilled off, and the residue fractionated *in vacuo*. The bromo-aldehyde (18 g.), b. p. 148—150°/40 mm., gave 5-bromo-2-thenaldehyde thiosemicarbazone, which melted at 182° after several recrystallisations from ethanol (Found: C, 27·0; H, 2·1. Calc. for $C_6H_6N_3S_2Br$: C, 27·3; H, 2·3%). The fact that the crude thiosemicarbazone did not melt sharply is taken to indicate the presence of isomeric bromo-2-thenaldehydes.

5-Bromo-2-thenaldehyde-4-oxo-Δ^2-thiazolin-2-ylhydrazone crystallised as colourless needles, m. p. 292°, from ethyl acetate (Found: C, 31·8; H, 2·3. $C_8H_6ON_3S_2Br$ requires C, 31·5; H, 2·0%); the *5-butyl*, needles, m. p. 196°, from ethanol (Found: C, 39·7; H, 3·7. $C_{12}H_{14}ON_3S_2Br$ requires C, 40·0; H, 3·9%), and the *5-hexadecyl analogue*, needles, m. p. 140° (ethanol) (Found: C, 54·1; H, 7·0. $C_{24}H_{38}ON_3S_2Br$ requires C, 54·5; H, 7·2%), were prepared.

The *nitriles* shown in the Table were prepared, with the exception of the *p*-nitrophenyl derivative, by shaking an ethanolic solution of equimolar amounts of the bromo-aldehyde and the appropriate arylacrylonitrile with a few drops of 20% aqueous sodium hydroxide, and recrystallisation of the precipitate from ethanol.

α-Aryl-β-(5-bromo-2-thienyl)acrylonitriles (II).

Aryl subst.	M. p.	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Phenyl	146°	$C_{13}H_8NSBr$	54·0	3·0	53·8	2·8
p-Tolyl	150	$C_{14}H_{10}NSBr$	55·2	3·2	55·3	3·3
p-Chlorophenyl	179	$C_{13}H_7NSBrCl$	47·8	2·2	48·1	2·2
p-Bromophenyl	183	$C_{13}H_7NSBr_2$	42·5	1·8	42·3	1·9
p-Methoxyphenyl	151	$C_{14}H_{10}ONSBr$	52·6	3·4	52·5	3·1
p-Nitrophenyl *	230	$C_{13}H_7O_2N_2SBr$	46·5	2·0	46·6	2·1
2-Thienyl	120	$C_{11}H_6NS_2Br$	44·5	2·3	44·6	2·0
2-Naphthyl	194	$C_{17}H_{10}NSBr$	60·1	3·2	60·0	2·9

* Prepared with piperidine as catalyst.

2 : 5-Dichloro-3-propionylthiophen (III; R = Et). To a solution of 2 : 5-dichlorothiophen (7 g.) and propionyl chloride (4·6 g.) in dry carbon disulphide (50 c.c.), aluminium chloride (7 g.) was added in small portions at room temperature, and the mixture left for 12 hr. with frequent shaking. After decomposition with water, the organic layer was washed with aqueous sodium hydroxide, then with water, dried (Na_2SO_4), and evaporated, and the residue distilled *in vacuo*; recrystallisation from ethanol gave colourless needles (6 g.), m. p. 60°, of the *ketone* (Found: C, 39·9; H, 2·8. $C_7H_6OSCl_2$ requires C, 40·2; H, 2·9%). When reaction was limited to 15 min. (which in the case of thiophen gave a yield above 90%), only negligible amounts of the

ketone were isolated. 2 : 5-*Dichloro*-3-*butyroylthiophen* (III; R = Pr), prepared similarly, formed a pale yellow oil, b. p. 143—144°/17 mm., n_D^{21} 1·5720 (Found: C, 43·3; H, 3·9. $C_8H_8OSCl_2$ requires C, 43·0; H, 3·6%). 2 : 5-*Dichloro*-3-*phenylacetylthiophen* was obtained as prisms (from ethanol), m. p. 67° (Found: C, 52·9; H, 3·3. $C_{12}H_8OSCl_2$ requires C, 53·1; H, 3·0%). The yield was particularly poor when the Friedel–Crafts reaction was performed with aromatic acid chlorides; from 2 : 5-dichlorothiophen (22 g.), benzoyl chloride (22 g.), and aluminium chloride (22 g.) in carbon disulphide (180 c.c.), 3-*benzoyl*-2 : 5-*dichlorothiophen* (5 g.) was obtained as a pale yellow oil, b. p. 192—194°/17 mm., n_D^{20} 1·6649 (Found: C, 51·5; H, 2·6. $C_{11}H_6OSCl_2$ requires C, 51·4; H, 2·3%). 2 : 5-*Dichloro*-3-2′-*thenoylthiophen* was a yellow oil, b. p. 210—212°/20 mm., n_D^{22} 1·6860 (Found: C, 41·4; H, 1·8. $C_9H_4OS_2Cl_2$ requires C, 41·1; H, 1·5%).

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353. *Reactions of Ammonia with Nickel*(II) *Cyanide.*

By E. E. AYNSLEY and W. A. CAMPBELL.

NICKEL cyanide in concentrated aqueous ammonia solution deposits dark blue crystals [1] of $Ni(CN)_2,4NH_3,2H_2O$ which, on exposure to air, quickly crumble to a pale blue powder and lose ammonia and water leaving stable $Ni(CN)_2,NH_3,H_2O$. Also, the material $Ni(CN)_2,NH_3$ obtained by the (almost complete) dehydration of the monoammine monohydrate, is only superficially like [2] that obtained by the almost complete removal of benzene from the clathrate compound $Ni(CN)_2,NH_3,C_6H_6$, a striking difference being that the dehydrated hydrate re-absorbs atmospheric moisture very rapidly but the decomposed clathrate compound does not.

We examined the reactions of anhydrous ammonia (gas and liquid) with nickel cyanide. When dry ammonia gas is passed over anhydrous nickel cyanide a strongly exothermic reaction occurs and a grey-violet diammine, $Ni(CN)_2,2NH_3$, is produced. When this is exposed to the atmosphere for a few hours one molecule of ammonia is replaced by one of water and stable $Ni(CN)_2,NH_3,H_2O$ is obtained. The same change, with effervescence, is rapidly brought about by adding the diammine to water. When kept in dry air in a desiccator ($CaCl_2$) for 12 hr., the diammine loses ammonia and leaves the monoammine, $Ni(CN)_2,NH_3$, which does *not* absorb moisture from the atmosphere. This points to some structural difference in the lattices of the two forms of $Ni(CN)_2,NH_3$.

When nickel cyanide is shaken with anhydrous liquid ammonia an unstable dark blue product is obtained which rapidly loses ammonia. The maximum increase in weight of the nickel cyanide suggests the formation of a tetrammine $Ni(CN)_2,4NH_3$ which after a few hours' standing in dry air leaves the stable monoammine, $Ni(CN)_2,NH_3$.

Experimental.—Preparation of nickel cyanide. Aqueous solutions containing " AnalaR " nickel sulphate (28 g. in 100 ml.) and potassium cyanide (13 g. in 100 ml.) were mixed and the precipitated hydrated nickel cyanide was recovered by centrifugation. The gelatinous product was washed and centrifuged four times to remove occluded potassium salts, and when dried at 140° gave yellow-brown anhydrous nickel cyanide.

Nickel was determined (*a*) by ignition to oxide and (*b*) as nickel dimethylglyoxime, total nitrogen by Kjeldahl digestion in a sealed tube, and ammonia by distillation from 0·1N-sodium hydroxide.

Preparation of $Ni(CN)_2,2NH_3$. Dry ammonia gas was passed over a few g. of nickel cyanide contained in a porcelain boat at laboratory temperature. The cyanide swelled considerably, much heat was evolved, and the *diammine* was left as a grey-violet powder [Found: Ni, 40·8; N, 38·1; NH_3, 22·9. $Ni(CN)_2,2NH_3$ requires Ni, 40·5; N, 38·7; NH_3, 23·5%].

Effect of water on $Ni(CN)_2,2NH_3$. (*a*) On exposure to the atmosphere the compound gradually lost ammonia and left odourless, pale blue $Ni(CN)_2,NH_3,H_2O$. (*b*) When the diammine was added to water it effervesced, forming the *monohydrate* [Found: Product from (*a*); Ni, 40·1; N, 28·2; NH_3, 11·4. Product from (*b*); Ni, 40·0; N, 28·4; NH_3, 11·3. $Ni(CN)_2,NH_3,H_2O$ requires Ni 40·1; N, 28·8; NH_3, 11·6%].

[1] Aynsley and Campbell, *J.*, 1957, 4137.
[2] Aynsley, Campbell, and Dodd, *Proc. Chem. Soc.*, 1957, 210.

Decomposition of $Ni(CN)_2,2NH_3$ *in dry air.* A weighed amount of the diammine was exposed overnight to dry air in a desiccator ($CaCl_2$). No colour change was observed but the *product* was $Ni(CN)_2,NH_3$ [Found: Ni, 45·8; N, 33·0; NH_3, 13·4. $Ni(CN)_2,NH_3$ requires Ni, 45·9; N, 32·9; NH_3, 13·3%. The loss in weight was 11·8% corresponding to 100% conversion].

Action of liquid ammonia on $Ni(CN)_2$. Excess of liquid ammonia was condensed on a weighed quantity of nickel cyanide and left for a few hours. The excess was allowed to boil off and the product, which was greater in bulk than the original cyanide and darker in colour than the diammine, was rapidly weighed. The weight increased, corresponding to the formation of a tetrammine $Ni(CN)_2,4NH_3$, but a complete analysis of the product was impossible because it rapidly lost ammonia. On exposure to dry air for a few hours, the monoammine was left.

KING'S COLLEGE, NEWCASTLE UPON TYNE, 1. [*Received, December 20th*, 1957.]

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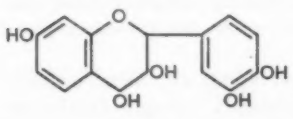
354. *The Identity of Gleditsin and Mollisacacidin.*

By J. W. CLARK-LEWIS and M. MITSUNO.

HEARTWOOD of the Japanese tree *Gleditsia* (or *Gleditschia*) *japonica* Miquel, also known as *G. horrida* Schneider, yields a crystalline substance (*ca.* 0·3%) termed gleditsin.[1] Typical leucoanthocyanidin properties indicated that gleditsin is the flavan-3 : 4-diol [2] (I) and not the corresponding flavan-3-ol or catechin as was originally supposed. Gleditsin is now shown to be identical with mollisacacidin [3] (I) by comparison of physical constants, by mixed melting point determinations and, more convincingly, by the close similarity of the infrared absorption curves determined with mulls. Each curve shows thirty-eight absorption bands in the range 2—15 μ, with minor differences appearing in only three of them, and this close correspondence suggests strongly that gleditsin is stereochemically as well as structurally identical with mollisacacidin. Stereochemical features of mollisacacidin (gleditsin) have yet to be determined, although it is tentatively regarded as a *cis*-glycol [3] like the related melacacidin.[4]



(I)

Experimental.—Gleditsin [1] crystallises as a dihydrate, $C_{15}H_{14}O_6,2H_2O$, m. p. 124—125° (decomp.), $[\alpha]_D^{12}$ +33·6° (in 50% acetone), and yields a trimethyl ether, m. p. 99—100·5° (sesquihydrate), 129·5—131° (anhydrous). Mollisacacidin dihydrate,[3] m. p. 125—130° (decomp.), $[\alpha]_D^{18}$ +12·6° (1% in MeOH), forms a trimethyl ether, m. p. 129° after sintering at 76—77°. A sample of mollisacacidin supplied by Dr. H. H. Keppler became red and decomposed gradually in the range 125—170° when heated in capillary tubes, and this behaviour was unchanged when mollisacacidin was mixed with gleditsin, which melted sharply at 125—126° (decomp.) under the same conditions. With a hot-stage microscope, thread-like filaments of both mollisacacidin and gleditsin were seen to soften and coalesce in the range 125—130° without obviously melting, and behaved similarly when mixed.

Gleditsin and mollisacacidin had the same R_F value (0·62) in butanol–acetic acid–water (5 : 1 : 4) and behaved similarly when sprayed with ammoniacal silver nitrate or with toluene-*p*-sulphonic acid (3% in ethanol).

Infrared absorption curves of Nujol mulls of gleditsin and mollisacacidin were determined with a Grubb-Parsons double beam spectrometer S4 (NaCl prism) and were closely similar throughout the recorded range (2—15 μ).

The authors thank Dr. H. H. Keppler for a sample of mollisacacidin and Dr. H. J. Rodda for determining the infrared spectra.

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UNIVERSITY OF TOYAMA, JAPAN. [*Received, December 27th*, 1957.]

[1] Mitsuno and Yoshizaki, *J. Pharm. Soc. Japan*, 1957, **77**, 557, 1280.
[2] Clark-Lewis, "Stereochemistry of Catechins and Related Flavan Derivatives," presented at a Symposium on Heterocyclic Chemistry, Canberra, September 2—4th, 1957 (*Chem. Soc. Special Publ.*, in the press).
[3] Keppler, *J.*, 1957, 2721.
[4] King and Bottomley, *J.*, 1954, 1399; King and Clark-Lewis, *J.*, 1955, 3384.

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